EXPRESS MAILING CERTIFICATE
"EXPRESS MAIL" Mailing Label No.: EL084652896US
Date of Deposit : January 31, 2001
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Box Patent Application, Washington, D.C. 20231
Typed or printed name of person signing this certificate:

Signed: Pat Simpson
PAT Simpson

PATENT

Detection of Methylated CpG Rich Sequences Diagnostic for Malignant Cells

This invention was conducted, at least in part, with government support under National Institutes of Health Grants No: P30 CA16058 and CA80912 awarded by the National Cancer Institute. The U.S. government has certain rights in the invention.

Background of the Invention

Diagnosis of cancer, classification of tumors, and cancer-patient prognosis all depend on detection of properties inherent to cancer, or malignant cells, that are absent in normal, nonmalignant cells. Since cancer is largely a genetic disease, resulting from and associated with changes in the DNA of cells, one important method of diagnosis is through detection of related changes within the DNA of cancer cells. Such changes can be of two types. The first type of change is a genetic change that occurs when the sequence of nucleotide bases within the DNA is changed. Base changes, deletions and insertions in the DNA are examples of such genetic changes. The second type of change in the DNA is an epigenetic change. Epigenetic changes do not result in nucleotide sequence changes, but rather, result in modification of nucleotide bases. The most common type of epigenetic change is DNA methylation.

In mammalian cells, DNA methylation consists exclusively of addition of a methyl group to the 5-carbon position of cytosine nucleotide bases. In the process, cytosine is changed to 5-methylcytosine. Cellular enzymes carry out the methylation events. Only cytosines located 5' to

guanosines in CpG dinucleotides are methylated by the enzymes in mammalian cells. Such CpG dinucleotides are not distributed randomly throughout the genome. Instead, there are regions of mammalian genomes which contain many CpG dinucleotides, while other areas of the genome contain few CpG dinucleotides. Such CpG-rich areas of the genome are called "CpG islands." Most often, CpG islands are located in the transcriptional promoter regions of genes.

Not all CpG islands are methylated. However, the methylation status of CpG islands (i.e., whether the CpG dinucleotides within a particular CpG island are methylated or not) is relatively constant in cells. Nevertheless, the pattern of CpG island methylation can change and, when it does, often a new, relatively stable methylation pattern is established. Such changes in methylation of CpG islands can be either increases or decreases in methylation.

Methylation of CpG islands in the promoter region of a few specific genes has been observed in some types of human cancer. However, at present it is still uncertain whether the methylation status of multiple CpG islands in the genomic DNA of subjects suspected of having cancer can be used as a diagnostic tool for determining whether or not tissue obtained from such subjects contain malignant cells.

Summary Of The Invention

The present invention relates to methods for identifying CpG islands which are diagnostic of one or more cancers in a subject. The method employs restriction landmark genomic scanning (RLGS) techniques and comprises separately digesting genomic DNA which has been obtained from malignant cells derived from a particular tumor tissue and genomic DNA which has been obtained from control cells derived from healthy tissue with an infrequently cutting restriction enzyme that is not capable of cleaving methylated recognition sites to provide a first set of DNA restriction fragments from the tumor tissue, referred to hereinafter as "malignant cell restriction fragments", and a first set of DNA restriction fragments from the healthy tissue, referred to hereinafter as "control cell restriction fragments"; attaching a detectable label to the ends of the malignant and control cell restriction fragments; digesting the labeled malignant and control cell restriction fragments with a second restriction enzyme; separating each set of restriction fragments on a gel; digesting the restriction fragments in each of the gels with a third more frequently cutting restriction enzyme; electrophoresing each set of restriction fragments in a direction perpendicular to the first direction to provide a first pattern of detectable malignant cell

restriction fragments and a second pattern of detectable control cell restriction fragments; and comparing the second pattern to the first pattern to identify control cell restriction fragments, hereinafter referred to as "diagnostic fragments", which are absent, or exhibit an decreased intensity of label in the first pattern. Such fragments comprise CpG islands that are methylated in the malignant cells. Such patterns are useful for characterizing tissue which is suspected of containing malignant cells. Preferably, each of the diagnostic fragments is then isolated and sequenced, at least in part. In one preferred embodiment, the first restriction enzyme is NotI. In another preferred embodiment, the first restriction enzyme is AscI. Advantageously, the present method permits the detection of numerous methylation sites within the entire genome. In accordance with the present method, applicants have determined that particular CpG islands are preferentially methylated in DNA obtained from tumor tissues of subjects diagnosed as having breast cancer, glioma, acute myeloid leukemia, primitive neuroectodermal tumors of childhood, colon cancer, head and neck cancer, testicular cancer, and lung cancer.

The present invention also provides isolated polynucleotides, referred to hereinafter as "CpG diagnostic polynucleotides", and isolated oligonucleotides referred to hereinafter as "CpG diagnostic oligonucleotides", which are useful for characterizing tissue samples obtained from a subject suspected of having gliomas, acute myeloid leukemia, primitive neuroectodermal tumors of childhood, or cancer of the breast, colon, head and neck, testicle or lung. The CpG diagnostic polynucleotides and oligonucleotidess both comprise a sequence which contains CpG islands that have been shown to be preferentially methylated in DNA that has been obtained from malignant cells of subjects diagnosed as having breast cancer, glioma, acute myeloid leukemia, primitive neuroectodermal tumor of childhood, colon cancer, head and neck cancer, testicular cancer or lung cancer. The CpG diagnostic polynucleotides are from 35 to 3000, preferably, 35 to 100 nucleotides in length, and comprise from 15 to 34, preferably 18 to 25 of the consecutive nucleotides contained with the sequences depicted in the accompanying DNA sequence listing, or sequences which are complementary thereto. The CpG diagnostic polynucleotides comprise two or, preferably, more CpG dinucleotides or dinucleotides which are complementary thereto. The CpG diagnostic oligonucleotides are from 15 to 34 nucleotides in length and comprise from 15 to 34 consecutive nucleotides contained within the sequences depicted in the sequence listing, or sequences which are complementary thereto. The CpG oligonucleotides comprises two or more CpG dinucleotides, or dinucleotides which are complementary thereto.

The present invention also relates to methods which employ the CpG diagnostic polynucleotides and oligonucleotides of the present invention to characterize tissue from patients suspected of having cancer. Such methods are based on the methylation status of CpG islands that have been shown to be preferentially methylated in DNA that has been obtained from tumor tissues of subjects diagnosed as having breast cancer, glioma, acute myeloid leukemia, primitive neuroectodermal tumor of childhood, colon cancer, head and neck cancer, testicular cancer and lung cancer. In one method, DNA which is isolated from suspected tumor tissue from a subject is digested into smaller fragments and reacted with a CpG diagnostic polynucleotide under stringent hybridization conditions. The reaction products are then assayed to determine the size or the sequence of the DNA fragment with which the CpG diagnostic polynucleotide has hybridized. The size or the sequence of the DNA fragment to which the CpG diagnostic polynucleotide has hybridized, hereinafter referred to as the "target DNA fragment", indicates whether the target DNA fragment comprises methylated or non-methylated CpG islands. The presence of methylated CpG islands in the target DNA fragment indicates that the DNA has been obtained from a tumor or neoplasm for which the diagnostic CpG polynucleotide serves as a diagnostic marker.

In another method the DNA from the suspected tumor tissue is treated with a chemical compound which converts non-methylated cytosines to a different nucleotide base. An example of such a compound is sodium bisulfite which converts non-methylated cytosines to uracil. The DNA is then reacted with at CpG diagnostic oligonucleotides under conditions which permit the CpG diagnostic oligonucleotide to hybridize with a complementary sequence in the DNA, referred to hereinafter as the "target sequence". The DNA is also reacted with a modified CpG diagnostic oligonucleotide. The modified CpG diagnostic oligonucleotide comprises a sequence that is complementary to a modified target sequence, i.e., a sequence in which the non-methylated cytosines in the target sequence are converted to a different nucleotide base, e.g. uracil, when treated with a chemical compound. The reaction products are then assayed to determine whether the DNA contains sequences which have hybridized with the CpG diagnostic oligonucleotide or with the modified CpG diagnostic oligonucleotide. Hybridization of the sample DNA with the CpG diagnostic oligonucleotide, as opposed to the modified CpG diagnostic oligonucleotide, indicates that the cytosines in the target sequence are methylated and that the DNA sample has been obtained from a tumor or neoplasm for which the CpG

oligonucleotide has been shown to serve as a diagnostic marker.

The present invention also relates to a method of identifying genes whose expression is increased or decreased in cancer cells.

Brief Description of the Figures

Fig. 1. Methylation detection in restriction landmark genomic scanning (RLGS) profiles. A, Diagram of the RLGS procedure showing the quantitative nature of methylation detection on NotI fragments displayed on RLGS profiles. Methylation detection in RLGS profiles depends on the methylation sensitivity of the endonuclease activity of NotI. Differences in digestion are assessed by radiolabelling the DNA at cleaved NotI sites. Following further endonuclease digestion, two-dimensional electrophoretic separation and autoradiography, the intensity of a DNA fragment on the resultant RLGS profile quantitatively reflects the copy number and methylation status of the NotI fragment. A priori, this allows NotI fragments containing single-copy CpG islands to be distinguished from the abundant NotI fragments present in repeat elements and rDNA sequences. B, A portion of an RLGS profile from normal peripheral blood lymphocyte DNA displaying nearly 2,000 single-copy NotI fragments and 15-20 high copy-number fragments. First-dimension separation of labeled NotI/EcoRV fragments extends from right to left horizontally. Following in-gel digestion with HinfI, the fragments are separated vertically downward into a polyacrylamide gel and autoradiographed. To allow uniform comparisons of RLGS profiles from different samples and different laboratories, each fragment is given a three-variable designation (Y coordinate, X coordinate, fragment number). The central region of the RLGS profile used for all comparisons described in this invention has 28 sections (1-5 vertically and B-G horizontally; the 4G and 5G sections were excluded due to high density and lower resolution of fragments). C, Enlarged view of profile section 2D, showing the numbers assigned to each NotI fragment. D, Analysis of the GC content and CpG ratio {(number of CpGs)/(number of guanines)(number of cytosines)}(number of nucleotides analyzed) of 210 non-redundant NotI/EcoRV clones containing the NotI/HinfI fragments seen in B and in other portions of the RLGS profile. Of 210 clones, 184 clones were randomly chosen and 26 corresponded to fragments which were frequently lost from tumor profiles. CpG islands have a GC content of greater than 50% and a CpG value of 0.6 or greater, relative to bulk DNA (average CG content of 40% and CpG ratio of 0.2). Nucleotide sequences were determined with

greater than 99% accuracy overall. An average of 377nt/clone were analyzed (not indicative of actual CpG island size). The average NotI/EcoRV clone size was approximately 2 kb.

Fig. 2. Fragment loss from RLGS profiles is due to methylation. Top, portions of the RLGS profiles obtained from normal tissue and from two tumors having NotI fragments with either decreased intensity or no change in intensity. Bottom, Southern-blot analysis of EcoRV (NotI: -) and EvoRV/NotI (NotI: +) restriction digested DNAs from a larger number of samples, including the samples at top. In samples without methylation in the NotI site, the probe detects a smaller fragment on double digestion with NotI and EcoRV. The quantitation from multiple Southern blots using a phosphorimager allowed the determination of a lower limit of reliable detection in RLGS profiles of 30% decreased intensity of the diploid NotI/EcoRV fragments. Presence (+) or absence (-) of the corresponding NotI fragment is indicated. N, normal tissue DNA; T, tumor tissue DNA. A, CpG-island locus 3C1 methylation in low-grade gliomas. B, CpG island locus 2C40 methylation in leukemias. C, CpG-island locus 3E24 methylation in PNETs of childhood. *, EcoRV fragment of approximately 13 kb with homology to the probe. BLAST searches using the NotI-EcoRV clone sequence identified a homologous BAC clone sequence lacking an internal NotI site, which accounts for the 13-kb fragment on the Southern blot.

Fig. 3. Heterogeneity in CpG-island methylation across tumors. RLGS profiles were generated from 98 primary human tumors and compared with profiles of either matched normal DNA (58 of 98 cases) or to multiple profiles of tissue type-matched normal DNA from unrelated individuals. Loss or decreased intensity of single-copy fragments in the tumors, relative to several neighboring unaltered NotI fragments, were detected by visual inspection of overlaid autoradiographs and confirmed in many cases by independent profiles of the same DNA samples. For each tumor type, the dot plots display the total number of methylated CpG islands (of 1,184 CpG islands analyzed) observed in each tumor. Under the assumption that the tumors are drawn from a homogeneous distribution, with all tumors having the same frequency of methylation, the loss distributions should be approximately Poisson. The colored curve represents the expected distribution. BRE, breast tumors; CLN, colon tumors; GLI, gliomas; HN, head and neck tumors; LEU, acute myeloid leukemias; PNET, primitive neuroectodermal tumors of childhood; TST, testicular tumors.

Fig. 4. Subsets of CpG islands are preferentially methylated. For each tumor type, the histograms display the number of tumors in which the particular CpG islands were methylated. Most of the 1,184 CpG islands were not methylated in any of the tumors (histogram bar at 0 is not shown), but several CpG islands were methylated in multiple tumors. The black line shows the expected distribution under the null hypothesis that the CpG islands have equal frequencies of methylation. Most of the tumor types show significant preferential methylation.

Detailed Description Of The Invention

In one aspect, the present invention relates to methods for identifying clones within a DNA library that can be used for cancer diagnosis and tumor classification, based on the methylation status of CpG dinucleotides contained within or closely adjacent to the specific clones. Such method employs methylation-sensitive restriction endonucleases (MSREs) and restriction landmark genomic scanning (RLGS) gels to identify new, differentially-methylated CpG islands within malignant cells obtained from patients diagnosed as having cancer. In accordance with the present invention, Applicants have identified 93 clones which can be used to determine whether a tumor biopsy from a patient contains benign or malignant cells.

To carry out such method, tissue (referred to hereinafter as "tumor tissue") which contains a tumor or neoplasm is obtained from a patient known to have a cancer. In some cases, the tumor tissue is obtained from a particular type of solid tumor which has bee surgically removed from the patient. In some cases, the tumor tissue is obtained from the hematopoietic system, such as for example, bone marrow or blood, of the patient. The tumor tissue will have been determined to be from either a benign or malignant tumor or neoplasm.

Separately, tissue (referred to hereinafter as "healthy tissue") which does not contain a tumor or neoplasm is obtained from a subject. The healthy tissue, may be obtained by surgically removing normal tissue from the patient or by surgically removing normal tissue from a healthy control subject who does not have cancer. The healthy tissue may also come from the hematopoietic system, such as for example, bone marrow or blood, of a healthy control subject. The healthy tissue will have been determined to be non-tumorigenic or non-neoplastic.

DNA is then isolated from both the tumor tissue and healthy tissue. If the tumor tissue is a solid tissue sample, such procedure may first comprise separating the individual cells contained

within the tissue from each other. For example, if the tissue samples were frozen after surgical removal from a patient, cells may be separated from one another by grinding the frozen tissue with a mortar and pestle. DNA is then isolated from the individual cells using procedures well known to those skilled in the art. Commonly, such DNA isolation procedures comprise lysis of the individual cells using detergents, for example. After cell lysis, proteins are commonly removed from the DNA using various proteases. The DNA is then commonly extracted with phenol, precipitated in alcohol and dissolved in an aqueous solution.

In the procedures which follow, the DNA obtained from the tumor tissue is treated separately from the DNA obtained from healthy tissue (i.e., the two DNAs are not mixed). The DNAs are separately analyzed using a method called restriction landmark genomic scanning (RLGS). The purpose is to analyze both DNAs separately. The two analyses are then compared in order to identify CpG islands that distinguish cancer cells from normal cells.

Both DNA samples are treated with restriction enzymes and the free ends that result from the restriction enzyme cleavage are labeled. However, since the isolated DNA is in linear pieces, there are free ends that exist before the DNA is cleaved with the restriction enzymes. To prevent these ends from being labeled, the ends, preferably, are blocked before restriction enzyme treatment. Such blocking can be done by addition of dideoxynucleotides and sulfur-substituted nucleotides to the free ends before treatment with restriction enzymes. Subsequently, when the DNA is cleaved by restriction enzymes and labeled, only the ends resulting from the restriction enzyme cleavage will be labeled.

After the reaction to block free ends, the DNA samples are cleaved with a first restriction enzyme that can be characterized as an infrequently cleaving, methylation-sensitive restriction enzyme. Examples of suitable first restriction enzymes are NotI, AscI, BssHII and EagI. As used herein the term "infrequently cleaving" refers to a restriction enzyme that is expected to cleave genomic DNA at intervals greater than 10 kilobases. For example, NotI is an infrequently cleaving restriction enzyme. NotI recognizes a nucleotide sequence of 8 base pairs (bp) in the genome (i.e., 5'GCGGCCGC3') and cleaves the DNA at this site. There are an estimated 4000-5000 of such NotI recognition sequences within the human genome. It is estimated that such recognition sequences are spaced at approximately 1 megabase (Mb) intervals within the genome. In contrast, a frequently cleaving restriction enzyme is expected to cleave the human genome at from 5-10 kb intervals. Such an enzyme will have approximately 100-times more

cleavage sites within the human genome than infrequently-cleaving enzymes. Such frequently cleaving enzymes usually recognize a nucleotide sequence of less than 8 bp in the genome and cleave the DNA at that site. However, not all restriction enzymes that have nucleotide recognition sequences of less than 8 bp are frequently cleaving enzymes. BssHII and EagI both have 6 bp recognition sequences but the recognition sequences for these two enzymes are spaced at intervals within the genome that are greater than 10 kb. "Methylation sensitive" as used herein refers to any enzyme that is unable to cleave DNA at its normal restriction site if one or more nucleotides within the recognition sequence is methylated. For example, the restriction enzyme NotI will cleave the 5'GCGGCCGC3' recognition sequence if the sequence does not contain a 5-methylcytosine. However, the NotI enzyme will not cleave this sequence if any of the cytosines have been methylated to become 5-methylcytosine.

Following digestion of the DNA with the first restriction enzyme, the ends of the DNA fragments are labeled. This can be done, for example, by attachment of nucleotides carrying a detectable label, such as a radiolabel, to the ends of the DNA sample. Typically, attachment is accomplished by filling in the recessed DNA ends left by cleavage with the first restriction enzyme such that the ends become blunt (i.e., non-recessed). Such end-filling reaction may employ deoxynucleoside triphosphates having a radiolabeled phosphate at the α phosphate position. Such labeled phosphate is preferably ^{32}P.

The labeled fragments from each sample are then cleaved with a second restriction enzyme. Such second restriction enzyme preferably cleaves human DNA at average intervals of between 5-10 kb. Such enzymes normally have a 6 bp recognition sequence. Preferably, the second restriction enzyme is not methylation sensitive. Examples of suitable second restriction enzymes are PstI, PvuI, EcoRV or BamHI. Cleavage of the DNA fragments with the second restriction enzyme provides a second set of fragments, labeled at the ends left by cleavage with the first enzyme. Many of such second fragments are smaller than the fragments resulting from cleavage with the first restriction enzyme.

The DNA fragments are then separated from one another. Preferably this separation is based on size. Preferably this separation is performed by first-dimension electrophoresis through an agarose tube-shaped gel of approximately 60 cm in length.

After electrophoresis through the tube-shaped gel, the DNA is digested within the gel with a third restriction enzyme. Such third restriction enzymes preferably have recognition

sequences of 4 or 6 bp. Such third restriction enzymes also have the property of being able to cleave DNA which is embedded within agarose. One such enzyme is HinfI.

After cleavage by the third restriction enzyme, the DNA is again separated based on size, preferably by electrophoresis through a polyacrylamide gel. Subsequently, the separated DNA fragments are detected based on the labeled ends of the DNA fragments. In those cases where the fragments are radiolabeld, detection is by autoradiography of the two-dimensional gel. Such autoradiography provides a pattern of DNA fragments or "spots." Such pattern is called an RLGS profile.

Each fragment on the RLGS profile obtained from using the DNA from healthy tissues is uniquely identified by its location on the autoradiograph (Y coordinate, X coordinate, fragment number). For each fragment location on the RLGS profile obtained from healthy tissue DNA, the identical location is observed on the RLGS profile obtained from tumor tissue DNA.

In a fragment by fragment comparison of RLGS profiles obtained from tumor tissue DNA with healthy tissue DNA, three different patterns are possible. First, for a given fragment on the healthy tissue RLGS profile, there may be a corresponding fragment at the same location, and of the same intensity, on the tumor tissue RLGS profile. This indicates that the first restriction enzyme cleaved both DNAs at the same sequences (Fig. 1A). This indicates that there were no differences in methylation of the NotI nucleotide recognition sequence of that fragment between the tumor tissue DNA and the healthy tissue DNA.

Second, for a given fragment on the healthy tissue RLGS profile, there may be no fragment at the same location on the tumor tissue RLGS profile. Such a pattern indicates that the first restriction enzyme did not cleave the tumor tissue DNA at the recognition sequence required to produce that specific fragment, but did cleave at such sequence within the healthy tissue DNA (Fig. 1A). This indicates that there was methylation within the NotI recognition sequence in the tumor tissue DNA but not in the healthy tissue DNA.

Third, for a given fragment on the healthy tissue RLGS profile, there may be a corresponding fragment at the same location on the tumor tissue RLGS profile, but the intensity of the fragment may be of decreased intensity. Such a pattern indicates that the first restriction enzyme cleaved one of two copies (i.e., the genome is diploid) of the tumor tissue DNA at the recognition sequence required to produce that specific fragment (Fig. 1A). In healthy tissue DNA, the first restriction enzyme cleaved both copies of the recognition sequence. This

indicates that there was methylation within one of two NotI recogniton sequences in the tumor tissue DNA.

Through comparisons of RLGS profiles obtained from healthy tissue DNA with profiles obtained from a large number of different tumor tissue DNAs, loss of specific fragments in multiple tumors can be associated with a specific type of cancer. Loss of such fragments from RLGS profiles, therefore, can be diagnostic for cancer in a subject. For example, loss of a specific fragment (i.e., methylation of the first restriction enzyme site at the end of said fragment) in a high percentage of tumor tissue DNAs from women known to have breast cancer can be diagnostic for breast cancer in subjects suspected of having the disease. To perform such a diagnostic analysis, DNA isolated from a patient suspected of having breast cancer would be analyzed by RLGS, as described above, to determine whether there was loss of one or more fragments in RLGS profiles that are known to be lost at high frequency in women known to have breast cancer. Similarly, loss of other specific fragments can be diagnostic for other cancers, such as for example, colon cancer, head and neck cancer, lung cancer, testicular cancer, neuroectodermal cancer, gliomas, acute myeloid leukemias, and others.

Loss of a specific fragment in RLGS profiles from multiple tumors can also be diagnostic of several types of cancer, rather than a single type of cancer. For example, loss of a specific fragment can occur in a high percentage of tumor tissue DNAs obtained from individuals with either breast, colon or lung cancer. Loss of such a spot from RLGS profiles using DNA obtained from a patient suspected of having cancer would be diagnostic for either breast, colon or lung cancer in that patient.

Isolated Polynucleotides and Oligonucleotides Diagnostic for Cancer

Individual DNA clones that contain the DNA present in each spot or fragment that makes up an RLGS profile can be obtained. This is done by constructing a DNA library of healthy tissue DNA that has been cleaved with the same first and second enzymes used to perform the RLGS gel analysis. Such DNA library will contain individual clones, each clone comprising DNA that is present in a single spot of the RLGS profile. The totality of clones within the library is representative of the combined DNA spots in the RLGS profile.

Individual clones within the library can be identified that contain the DNA of each spot on the RLGS profile. This can be done by taking DNA from one or a few individual clones of the DNA library and mixing it with healthy tissue DNA, before RLGS analysis is begun. When

this mixture of DNAs is used to produce an RLGS profile, the intensity of the spots that contain the same DNA as the individual clones added to the mixture will be increased. By performing multiple analyses of this type, each spot on an RLGS profile can be matched up with a DNA clone within the library. The result of such an analysis is an ordered human genomic library of restriction fragments containing the same subset of genomic fragments as those displayed on RLGS profiles. In such ordered genomic libraries, an individual library clone corresponding to any spot or fragment in an RLGS profile can be rapidly located.

To design diagnostic CpG polynucleotides and oligonucleotides, the sequence of the DNA within each clone (referred to hereinafter as a "diagnostic clone") that corresponds to a spot that is absent or exhibits decreased intensity on the RLGS profile of the DNA from malignant tumor tissue is sequenced using standard techniques. Once sequence information is obtained, regions comprising multiple CpG dinucleotides are located. Such regions serve as the target sequence for the CpG polynucleotides and oligonucleotides.

The CpG polynucleotides are from 35 to 3000 , preferably from 35 to 1500 nucleotides in length and comprise two or, preferably, more CpG dinucleotides or dinucleotides which are complementary thereto. The CpG diagnostic oligonucleotides are from 15 to 34 nucleotides, preferably from 18 to 25 nucleotides, in length and comprise at least two CpG dinucleotides or dinucleotides which are complementary thereto. The CpG diagnostic polynucleotides and oligonucleotides each comprise a sequence which is substantially complementary to target sequences containing CpG islands that are known to be preferentially methylated in the DNA from one or more types of cancer cells. "Substantially complementary" means that there is enough complementarity between the CpG diagnostic polynucleotides or oligonucleotides and the target sequence so that hybridization occurs between the CpG diagnostic polynucleotides and oligonucleotides under stringent conditions, preferably under highly stringent conditions. Such assays include hybridization assays, such as for example Southern analysis, where the sample DNA is reacted with the CpG diagnostic polynucleotide under stringent hybridization conditions.

The term "stringent conditions, as used herein, is the "stringency" which occurs within a range from about Tm-5 (5 below the melting temperature of the probe) to about 20 C below Tm. "Highly Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 g/ml denatured,

sheared salmon sperm DNA, followed by washing the filters in 0.2x SSC at about 65 degree C. As recognized in the art, stringency conditions can be attained by varying a number of factors such as the length and nature, i.e., DNA or RNA, of the probe; the length and nature of the target sequence, the concentration of the salts and other components, such as formamide, dextran sulfate, and polyethylene glycol, of the hybridization solution. All of these factors may be varied to generate conditions of stringency which are equivalent to the conditions listed above.

Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lower stringency); salt conditions, or temperature. For example, moderately high stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2 M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reag ents may require modification of the hybridization conditions described above, due to problems with compatibility.

Such assays also include polymerase chain reactions (PCR) where the sample DNA and the diagnostic CpG oligonucleotides are reacted, preferably under conditions which result in the synthesis of a single PCR product. Computer programs, such as for example, the "Primer3" program that can be accessed at "http://genome.wi.mit.edu/cgi-bin/primer/primer_3www.cgi" can be used to determine the size and sequence of the CpG diagnostic oligonucleotides. Optimum conditions are determined empirically.

The CpG diagnostic polynucleotides and oligonucleotides are made using standard techniques. For example, these polynucleotides and oligonucleotides may be made using commercially available synthesizers.

Diagnostic Methods

In another aspect, the present invention relates to methods which use the CpG diagnostic

polynucleotides and oligonucleotides to characterize tissue samples from a subject suspected of having cancer, referred to hereinafter as test sample DNA. To do this, DNA is isolated from the cells of the tissue sample of the patient. Preferably, DNA that serves as a control is also obtained from healthy tissue of the test subject or a control subject as described previously. The diagnostic methods comprise reacting the test sample DNA with the diagnostic CpG polynucleotide or oligonucleotide and assaying the products that are formed as the result of the reaction. In some cases, the sample DNA is digested into smaller fragments prior to reaction with the CpG diagnostic polynucleotides or oligonucleotides. In some cases, a portion of the test sample DNA is first reacted with a chemical compound, such as for example sodium bisulfite, which converts methylated cytosines to a different nucleotide base.

Southern Blot Analysis

One such method for diagnosing cancer in a patient involves cleavage of the test sample DNA with a methylation sensitive enzyme, then Southern blot analysis of said cleaved DNA using a CpG diagnostic polyncleotide or oligonucleotide as a probe. For example, the DNA from the patient and the control, healthy tissue DNA are separately cleaved with a methylation-sensitive restriction endonuclease, such nuclease being the same first restriction enzyme used to identify the diagnostic spot in the RLGS profile that corresponds to the CpG diagnostic polynucleotide or oligonucleotide. After cleavage, the test sample and control DNAs are electrophoretically separated by size in different lanes of the same agarose gel and blotted to a membrane that can be used in hybridization, such as for example, nitrocellulose or nylon. The membrane is then used in a hybridization reaction with a labeled CpG diagnostic polynucleotide or oligonucleotide. The labeled CpG diagnostic polynucleotide or oligoneucleotide will hybridize to complementary DNA sequences on the membrane. After hybridization, the location on the membrane where the probe hybridized to the control and patient DNAs is visualized. Such locations will identify DNA fragments or bands within the control and patient DNAs containing the same sequence as the CpG diagnostic polynucleotide or oligonucleotide. Hybridization of the probe to a fragment within the patient DNA that is of higher molecular weight than that of the fragment within the control DNA to which the probe hybridized, indicates that a restriction endonuclease cleavage site flanking the target sequence of the CpG diagnostic polynucleotide or oligonucleotide was not cleaved due to methylation. Such result indicates that the tissue is from a cancer for which the CpG diagnostic polynucleotide or oligonucleotide serves

as a diagnostic tool.

A second method for diagnosing cancer in a patient involves cleavage of patient DNA with a methylation-sensitive restriction endonuclease, such nuclease being the same first restriction enzyme used to identify the diagnostic spot in the RLGS profile that corresponds to the fragment. Such nuclease will cleave the patient DNA at the diagnostic recognition sequence only if the DNA is unmethylated. Using nucleotide information derived from sequencing of the library clone corresponding to the diagnostic spot on the RLGS gel, primers for PCR are selected that span the diagnostic recognition sequence. Using the primers, PCR is performed on the DNA. PCR amplification of the sequences will be successful only if the diagnostic nucleotide sequence in the patient DNA had been methylated and was not cleaved by the enzyme. Successful PCR amplification, therefore, is indicative of cancer in the patient.

Methods Employing a Chemically-Modified DNA Test Sample

Another group of methods for diagnosing cancer in a patient using CpG diagnostic polynucleotides and oligonucleotides are based on treatment of patient DNA with sodium bisulfite which converts all cytosines, but not methylated cytosines, to uracil. The bisulfite converted patient DNA can then be analyzed in a number of different ways. One method of analysis is direct sequencing of the DNA to determine whether the sequence contains cytosine or uracil. Such DNA sequencing requires primers adjacent to the sequenced region to be made. Such primers would be based on DNA sequence information obtained from the diagnostic RLGS spots.

Another method of analyzing bisulfite converted patient DNA is a method called "methylation sensitive PCR" (MSR). In MSR, primers are designed to comprise a sequence which is substantially complementary to the the CpG islands which are known to be preferentially methylated in DNA of cells found in one or more type of tumor tissues. Two sets of PCR primers are made to ~~emcompass~~ encompass this region. One set of primers is designed to be complementary to the sequence that was changed by bisulfite (i.e., cytosines that were originally unmethylated and changed to uracil). As discussed above, these are the modified CpG diagnostic oligonucleotides. A second set of primers is designed to be complementary to the same sequence that was not changed by bisulfite (i.e., cytosines that were methylated and not changed to uracil). As discussed above these are the unmodified CpG diagnostic oligonucleotides, i.e the oligonucleotides which containe at least two CpG dinucleotides or

dinucleotides which are complementary thereto. Two sets of PCR reactions are then run, one reaction with each set of primers, using DNA from the subject as the template. In the case where cytosines within the target sequence of the subject DNA are not methylated, the target sequence will be modified by the chemical reaction and the primers complementary to the modified sequence, i.e., the modified CpG diagnostic oligonucleotides, will produce a PCR reaction product while the primers complementary to the methylated sequence, i.e., the unmodified CpG diagnostic oligonucleotides, will not produce a PCR product. In the case where cytosines within the target sequence of the subject DNA are methylated, the target sequence will not be altered by the reaction with the sodium bisulfite, and the primers complementary to the unaltered sequence, i.e., the unmodified CpG diagnostic oligonucleotides, will produce a PCR reaction product while the modified CpG diagnostic oligonucleotides, which are complementary to the modified target sequence (i.e., unmethylated sequence) will not produce a PCR product

A modification of MSR is bisulfite treatment of patient DNA and PCR amplification of said DNA using primers designed to amplify either methylated or unmethylated sequences. The PCR product is then digested with a restriction enzyme that will cleave or not depending on whether said product contains uracil (rather, thymidine, the complement of uracil; found in PCR product if original patient DNA contained unmethylated cytosine) or cytosine (found in PCR product if original patient DNA contained methylated cytosine).

Another technique referred to as MS-SnuPE, uses bisulfite/PCR followed by primer extension, where incorporation of C (vs. T) denotes methylation.

Methods of Identifying Genes

In another aspect of the invention, the CpG diagnostic polynucleotides and oligonucleotides can be used as probes to to identify genes whose expression is increased or decreased in cancerous tissues. To do this, CpG diagnostic polynuceotides are reacted with individual clones of the DNA library. The clones which hybridize with the CpG diagnostic polynucleotide can then be analyzed to determine if they contain an open reading frames that could encode proteins. To determine if the CpG diagnostic polynucleotide hybridizes with the promoter region of a known gene, the open reading frame sequence is analyzed by searching existing DNA databases. For example, GenBank databases can be searched using the BLAST algorithm. If no known genes that correspond to a library clone is found, the sequence can be

searched for open reading frames that could encode a protein. Such searching can be performed using commercially available sequence analysis programs commonly known to those skilled in the art. GCG is an example of one such program.

Sequences from clones of the DNA library that contain either known genes or open reading frames can be used as probes to determine whether genes encoded by the sequences are expressed in tumor tissues as compared to control, healthy tissues. To do this, RNA, preferably messenger RNA (mRNA) is isolated from healthy tissue and from tumor tissue from which it is desired to test expression. Such RNA is examined for the presence of expressed transcripts encoded by the sequences obtained from the library. Examination for the presence of expressed transcripts can be performed using a number of methods. One method is Northern blotting where the isolated RNA is separated by size using gel electrophoresis and then blotted to a hybridization membrane. A fragment, polynucleotide or oligonucleotide from the sequence obtained from a library clone is labeled and then used to probe the hybridization membrane containing the size-separated RNA. Detection of hybridization of the probe to the membrane indicates presence of a transcript encoded by the sequence and indicates expression of the gene encoded by that sequence.

Another method to examine isolated RNA for the presence of expressed transcripts is to use RT-PCR analysis. In such analysis, primers are designed and made that span a region of the gene whose expression is to be tested. The isolated RNA is reverse transcribed into DNA using reverse transcriptase. Such DNA is then amplified with the designed primers using PCR. PCR products are visualized after electrophoresis. The presence of PCR products on the gel indicates that the gene encompassed by the designed primers was expressing RNA transcripts. Such analysis can identify and determine genes whose expression is changed in cancer cells as compared to normal, non-cancerous cells.

The following examples are for purposes of illustration only and are not intended to limit the scope of the invention as defined in the claims which are appended hereto.

Examples

Example 1. Identification of diagnostic markers using NotI and RLGS

A. Isolation and enzymatic processing of genomic DNA

Tissue from solid tumors was obtained as surgical tissue samples. Where possible, surrounding non-tumor tissue was taken and used as a control. Where it was not possible to obtain patient-matched normal tissue, normal tissue from multiple patients was used. Tissue samples from patients with acute myelogenous leukemis (AML) consisted of either bone marrow aspirates or peripheral blood. Normal samples were obtained from the same patients who were in remission after chemotherapy.

The surgically removed tissues were quickly frozen in liquid nitrogen and stored at -80°C prior to isolation of DNA. When DNA was ready to be isolated, 2 ml of lysis buffer (10 mM Tris, pH 8.0; 150 mM EDTA, 1% sarkosyl) was added to 100-300 mg of tissue in a 50 ml Falcon tube and frozen in liquid nitrogen. The frozen mixture was then removed from the tube, wrapped in aluminum foil, and quickly broken into pieces with a hammer. The broken pieces of cells were transferred to a chilled mortar and ground to a powder with a chilled pestle. For peripheral blood samples, cells were separated on a sterile Histopaque-1077 (SIGMA) gradient and stored at -80°C before DNA isolation.

Cells were transferred to a 50 ml tube and 15-25 ml of lysis buffer containing 0.1 mg proteinase K per ml of lysis buffer was added and mixed using a glass rod. The mixture was incubated at 55°C for 20 min with gentle mixing every 5 min. The mixture was then placed on ice for 10 min. Subsequently, an equal volume of PCI (phenol:chloroform:isoamylalcohol in a ratio of 50:49:1) was added and the tubes containing the mixture were gently rotated for 30-60 min. The tubes were then centrifuged for 30 min at 2500 rpm and the separated, aqueous phase was transferred to a new 50 ml tube using a wide-bore pipette. The PCI extraction was repeated one time. The collected aqueous phase containing the DNA was transferred to dialysis tubing and dialyzed against 4 L of 10 mM Tris, pH 8 for 2 hr. The dialysis tubing was then transferred into fresh 10 mM Tris and dialyzed overnight at room temperature. One additional dialysis was performed in fresh 10 mM Tris for an additional 2 hr. The DNA was then transferred from the dialysis tubing to 50 ml tubes and RNase A was added to a final concentration of 1 μg/ml. The mixture was incubated at 37°C for 2 hr. Subsequently, 2.5 volumes of 100% ethanol were added

to the DNA and the mixture was gently rotated. The insoluble DNA was transferred to a microfuge tube, centrifuged briefly, and the remaining alcohol removed. The pellet was briefly dried in air. The DNA in the pellet was resuspended to a final concentration of 1 μg/μl. Such isolated DNA had an average size of 200-300 kb.

The isolated genomic DNA was blocked at ends where the DNA had been sheared. Blocking was done by addition of dideoxynucleotides and sulfur-substituted nucleotides. In a 1.5 ml tube, 7 μl of genomic DNA solution was added along with 2.5 μl of blocking buffer (1μl 10X buffer 1, 0.1μl 1 M DTT, 0.4 μl each of 10 μM dGTPαS, 10 μM ddATP, 10 μM ddTTP, and 0.2 μl 10 μM dCTPαS; buffer 1 consists of 500 mM Tris, pH 7.4, 100 mM $MgCl_2$, 1 M NaCl, 10mM DTT) and 0.5 μl DNA polymerase I. The mixture was mixed thoroughly and incubated at 37°C for 20 min. The mixture was then incubated at 65°C for 30 min to inactivate the polymerase. The reaction was then cooled on ice for 2 min. The DNA was digested with NotI by adding to the sample, 8μl of 2.5X buffer 2 (20X buffer 2 is 3 M NaCl, 0.2% Triton X-100, 0.2%BSA) and 2μl (10 U/μl) of NotI. The sample was incubated at 37°C for 2 hr. The DNA was then radioactively labeled. This was done by adding to the sample 0.3 μl 1 M DTT, 1 μl [α-^{32}P]-GTP, 1 μl [α-^{32}P]-dCTP and 0.1 1 μl[α-^{32}P]-GTP Sequenase ver 2.0 (13 U/μl). The mixture was incubated at 37°C for 30 min. The DNA was then digested with EcoRV by adding to the sample 7.6 μl second enzyme digestion buffer (1 μl 1 mM ddGTP, 1 ul 1 mM ddCTP, 4.4 μl ddH_2O, 1.2 μl 100 mM $MgCl_2$) and 2 μl EcoRV (10 U/μl). The mixture was incubated at 37°C for 1 hr. Then, 7 μl of 6X first-dimension loading dye (0.25% Bromophenol Blue, 0.25% Xylene Cyanol, 15% Ficoll type 400) was added.

B. First dimension gel set-up and electrophoresis

To make the 60 cm long agarose tube-shaped gel, a gel holder was made. To do this, a sharp razor was used to cut one end of PFA-grade teflon tubing (PFA 11 thin wall, natural; American Plastic, Columbus, Ohio) at an angle to make a bevel. The beveled end of the tubing was fed into glass tubes (4 mm inner diameter, 5 mm outer diameter, 60 cm long). Using a hemostat, the beveled end was pulled up through the tapered end of the glass rod until it protruded 2 to 4 cm. The tubing was cut horizontally at the same end, leaving a 2 mm protrusion (this is the top of the gel holder). The opposite end was cut horizontally, leaving a 5 to 6 cm protrusion from the glass tube. The gel holder was inverted and the top protruding end was

pressed firmly against a hot metal surface (metal spatula heated by a Bunsen burner) to fold the edges of the teflon outward onto the rim of the glass support. A rubber stopper with cored center was pulled over the top end of the gel holder until it was just past the taper of the glass rod. A two-way stopcock was attached to a 10 ml syringe and then to the gel holder via 2 to 3 cm of flexible tubing. The stopcock valve was adjusted to the open position.

Then, to a clean 200 ml glass bottle was added, 60 ml 2X Boyer's buffer (20X is 1 M Tris, 360 mM NaCl, 400 mM sodium acetate, 40 mM EDTA) and 0.48 g Seakem GTG agarose (0.8%). The mixture was heated in a microwave oven until the agarose was dissolved. The mixture was then equilibrated to 55°C in a water bath. With the stopcock valve in the open position, the protruding teflon tube was lowered into the molten agarose solution. The gel solution was suctioned into the gel holder until the gel solution reached 1-2 cm from the top of the gel holder. The stopcock valve was then closed. Keeping the gel upright, the gel was suspended from a ring stand. The gel was allowed to solidify for 20 min.

The stopcock valve was then opened and the syringe and connecting tubes were removed from each gel. After adding 2X Boyer's buffer to the bottom of the first dimension gel apparatus (C.B.S. Scientific), the gels were lowered into the first dimension gel apparatus, seating the rubber stopper firmly into the appropriate holes in the top portion of the apparatus. The top chamber was filled with 2X Boyer's buffer.

Between 1.0-1.5 μg of DNA was loaded onto each gel. The sample was electrophoresed at 110 V for 2 hr, and then 230 V for 24 hr.

C. In-gel digest

After the DNA was electrophoresed in the first dimension in the agarose tube gel, the DNA was further digested with an additional restriction endonuclease so it could be electrophoresed in the second dimension. In order to perform this additional endonuclease digestion, the buffer and gel holders were removed from the first dimension apparatus. The gel was extruded into a pan containing 1X buffer K (10X buffer K is 200 mM Tris, pH 7.4, 100 mM MgCl2, 1 M NaCl) by forcing the gel out through the bottom of the gel holder. This was accomplished using a 1 ml syringe fitted with a pipet tip and filled with buffer K. The tip was firmly inserted into the top of the gel holder and the plunger depressed until the gel began to come out through the bottom of the gel holder. The 1 ml syringe was replaced with a 5 ml

syringe, and the plunger was depressed until the entire gel was expelled. With a razor, a bevel was cut in the low molecular weight end of the gel and a horizontal cut was made at the high molecular weight end so that the gel was approximately 43 cm in length. The gel length was now the same as the width of the second dimension gel.

The gel was placed into a separate 50 ml tube containing 40 ml of 1X buffer K. The tube was incubated for 10 min at room temperature. The buffer was poured off and the gel incubated in 1X buffer K for an additional 10 min. The buffer K and gel was poured into a pan containing fresh buffer K. Using a 10 ml syringe attached to restriction digest tubing (PFA grade teflon, 9, thin wall, natural; 2.7 mm inner diameter and approximately 3.3 mm outer diameter; American Plastic, Columbus, Ohio), via a 1 to 2 cm segment of flexible tubing, the gel was suctioned into the digest tubing, low molecular weight (beveled) end first. The gel was suctioned into the digest tubing by placing the end of the tubing in line with the beveled end of the gel and pulling the syringe plunger. The tubing was positioned vertically, with the syringe at the bottom and remaining buffer from the tubing was suctioned into the syringe.

In a clean tube, a 1.6 ml mix of 1X HinfI restriction enzyme buffer (50 mM NaCl, 10 mM Tris pH 7.9, 1 mM DTT), 0.1 % BSA, and 750 U of HinfI restriction enzyme was made. The open end of the digest tubing was placed into the tube containing restriction digestion solution. Holding the syringe end up, suction was applied until a small amount of digestion solution appeared in the syringe. The digest tubing was removed and both ends were oriented upward in a U-shape. The syringe was removed and the two ends of the tubing were attached to form a closed circle. This was placed in a moist chamber and incubated at 37°C for 2 hr.

D. Second dimension electrophoresis

The digested DNA was now run in the second dimension using a 5% non-denaturing acrylamide gel with a 0.8% agarose spacer. To do this, the second dimension gel apparatus (C.B.S. Scientific) was first assembled. All glass plates were cleaned thoroughly and the non-beveled face of each plate was coated with Gelslick or Sigmacote (only once every 10 uses). The back half of the apparatus was laid horizontally on a table top with the upper buffer chamber hanging over the table edge. The two small clear plastic blocks were inserted at the bottom corners of each apparatus. A glass plate was placed in the apparatus, beveled edge facing upward and near the upper buffer chamber, followed by two spacers, one along each side. Glass

plates and spacers were added in this manner until the fifth plate had been added. After the third plate, flexible Tygon tubing was slid down the side channel of the apparatus, with a bevel cut in the leading end of the tubing. The other end was cut, leaving approximately 10 cm protruding from the apparatus. The Plexiglas "filler" sheet was placed over the fifth glass plate. The front half of the apparatus was positioned by aligning the screw holes of the front and back half. These were secured with the teflon screws. The oblong oval "windows" at the lower, front face were sealed with Plastic tape (Scotch brand). The apparatus was stood upright in the lower buffer chamber.

Using a three-way stopcock, the gel apparatus tubing was attached in series with a 2 L reservoir and a 60 ml syringe was attached to the remaining stopcock outlet. The tubing was attached to the 2 L reservoir through a bottom drain (a 2 L graduated cylinder was used). The reservoir was secured above the gel apparatus to allow for gravity flow. The stopcock valve was adjusted to allow liquid to flow between the 2 L reservoir and the 60 ml syringe. Once the TEMED was added, the acrylamide solution (1X TBE, pH 8.3, 96.9 g acrylamide, 3.3 g bis-acrylamide, 1.3 g ammonium persulfate and 700 µl TEMED in a total volume of 2 L) was poured into the 2 L reservoir. The syringe plunger was pulled down to the 50 ml mark. The plunger was depressed to push the air out of the upper tubing. Once all air was removed, the valve was adjusted so that all three ports were open. Acrylamide flowed into the apparatus, filling all four gels simultaneously from the bottom upward. The flow was stopped when the level reached 3 mm from the top edge of the glass plates. The solution was allowed to settle for 2 to 3 minutes. After the valve leading to the gel apparatus had been closed, the syringe and reservoir were detached.

The ends of the in-gel digest digest tubing were separated and the first dimension gel was extruded into a pan containing 1X TBE, pH 8.3. The gel was transferred to a 50 ml tube containing 40 ml 1X TBE, pH 8.3. This was incubated for 10 min at room temperature, replaced with fresh TBE, and incubated for an additional 10 min. The first dimension gel was placed in a horizontal position across the beveled edge of each glass plate. Once all gels were in place, the space between the agarose gel and the top of each polyacrylamide gel was filled with molten 0.8% agarose (equilibrated to 55°C). This connecting agarose was allowed to solidify for 10 to 15 min and then 250 µl second dimension loading dye (1X TE, pH 8.3, 0.25% Bromophenol Blue, 0.25% Xylene Cyanol) was added along the length of each gel. Then 1X TBE, pH 8.3 was

added to the upper and lower buffer chambers and electrophoresis was carried out at 100 V for 2 hr and then at 150 V for approximately 24 hr.

Buffers were then removed and the apparatus was disassembled. Each gel was lifted from the plates by overlaying with Whatmann paper cut to size for autoradiographic or phosphorimager cassettes. The perimeter of the paper was traced with the edge of a plastic ruler, removing any excess gel. The Whatmann paper and gel were lifted and placed, gel side up, on a second piece of Whatmann paper. This was overlaid with saran wrap and a third piece of Whatmann paper was added to the top and saran wrap was folded over the top of the Whatmann paper. This was placed in a gel drier, in the same orientation, for 1 hr at 80°C while applying a vacuum. The lower and upper Whatman paper was then removed, saran wrap folded under the remaining paper and exposed to X-ray film (BioMax MS).

E. RLGS spots resulting from methylation-sensitive restriction enzymes identify CpG islands

Using this methodology, an RLGS profile of DNA from human cells produces a pattern displaying approximately 2,000 spots. Fig. 1B, for example, shows such an RLGS profile from normal peripheral blood lymphocyte DNA. First-dimension separation of labeled NotI/EcoRV fragments extends from right to left horizontally. Following in-gel digestion with HinfI, the fragments were separated vertically downward into a polyacrylamide gel and autoradiographed. To allow uniform comparisons of RLGS profiles, spots were defined based on their location in the gel by assigning each spot a three-variable designation (Y coordinate, X coordinate, fragment number). This can be more easily seen in the enlarged portion of section 2D of the RLGS profile (Fig. 1C) showing the numbers assigned to each spot.

From a set of 1,567 NotI spots comprising the central portion of the RLGS profile of normal DNA, 392 spots were eliminated from all analyses on the basis of having more than diploid intensity, less than diploid intensity, or a degree of positional overlap with neighboring fragments. In addition, a small fraction of loci in individual tumor profiles was not able to be analyzed due to poor local gel quality. In normal DNA profiles, the less-than-diploid copy-number intensities can result from polymorphism, partial methylation or spots derived from sex chromosomes. Thus, the analyzed spots were of diploid copy number in most samples. Tumor tissue and healthy tissue DNA profiles were compared by visual inspection of overlaid autoradiographs. In those cases in which matched normal tissue was not available, tumor

profiles were compared with profiles matched for tissue type of four to five unrelated individuals. Each CpG island was defined as unmethylated or methylated (a visually apparent decrease in intensity on the RLGS profile, which, through corroboration with Southern-blot data for 26 CpG island loci and more that 100 loss events, corresponded to a 30% or greater level of methylation).

To determine if the NotI restriction sites which produced the RLGS spots, had characteristics of authentic CpG islands, DNA from 210 of the NotI/EcoRV RLGS spots was partially sequenced. This was possible because each spot on the human NotI/EcoRV RLGS profile had previously been assigned to a clone from a NotI/EcoRV genomic plasmid library (see description earlier in the specification). Of the 210 spots, 184 were randomly chosen. Another 26 spots were chosen because they were frequently lost from RLGS profiles from human tumors, suggesting that cytosine nucleotides within the NotI sequence of that spot were methylated in the tumor. From the sequences derived from these clones, the GC content (%GC) was plotted against the CpG ratio for each clone (Fig. 1D; CpG ratio = [(number of CpGs)/(number of guanines)(number of cytosines)(number of nucleotides analyzed)]). CpG islands have a GC content of greater than 50% and a CpG value of at least 0.6. Fig. 1D shows that, of 210 clones sequenced, 197 (94%) had sequence characteristics consistent with CpG-island DNA.

F. Tumor tissue samples analyzed

DNA used to perform the RLGS analyses was obtained from 98 primary human tumors and, where possible, matched normal samples. These samples were from 8 broad tumor types; breast, colon, gliomas, head and neck, acute myeloid leukemias, primitive neuroectodermal tumors (PNETs) and testicular.

Fourteen breast cancers included 2 adenocarcinomas, 2 lobular carcinomas and 10 ductal carcinomas. The samples were from obtained the Cooperative Human Tissue Network (CHTN). All tumors were from females, 38-89 years of age (average of 54 years). Breast tissue adjacent to the tumor was available for 6 of 14 cases, and 8 tumor profiles were compared with 4 breast samples from the matched sets.

Colon tumors were obtained from Roswell Park Cancer Institute and classified according the American Joint Committee on Cancer staging manual. The 8 primary tumors included 1 stage I tumor, 2 stage II tumors, 2 stage III tumors and 3 stage IV tumors. Patient ages ranged

from 49 to 77 years (average of 63 years). Normal adjacent colon mucosa samples were obtained for all tumors.

Fourteen gliomas, including 12 World Health Organization (WHO) grade II astrocytomas and 2 WHO grade III anaplastic astrocytomas, from Saitama Medical School, the University of Tokyo, Teikyo University School of Medicine, Komagome Metropolitan Hospital and the University of Washington, Seattle. Patients included 10 females and 4 males with an age range of 7-57 years (average of 34 years). Brain tissue adjacent to the tumor was also obtained for 1 WHO grade II and 1 WHO grade III tumor. Twelve cases were compared with 3 unmatched normal brain samples and with the 2 brain samples from the matched sets.

Fourteen head and neck squamous cell carcinomas were obtained through the CHTN. Tumors were from 11 males and 3 females. Patients were 42-77 years of age (average of 57 years). Tissue adjacent to the tumor was available for 12 of 14 cases, and 2 tumors were compared with 4 samples from the matched sets.

Nineteen acute myelogenous leukemia samples (3 bone marrow aspirates and 14 peripheral blood) from the Cancer and Leukemia Group B Tissue Bank. Samples were classified according to the French-American-British system. Samples were obtained from patients at the time of initial diagnosis with AML and again at complete remission (24-154 days, average 45 days) after induction chemotherapy. Samples were from 14 males and 3 females. Patients were 22-61 years of age (average 40 years). All cases were compared with matched samples (either peripheral blood lymphocytes or bone marrow, but always matched with the origin of the cancer sample) obtained at remission.

Twenty-two PNETs, including 17 medulloblastomas and 5 supratentorial PNETs, through the CHTN, Pediatric Division. Tumors were from 15 males and 7 females. Patients were 2-26 years of age, with peak ages between 3 and 6 years. All tumors were WHO grade IV. Matched peripheral blood lymphocytes were available for 6 of 22 cases, and 18 samples were compared with unmatched normal cerebellum DNA.

Nine testicular tumors included 6 seminomas and three nonseminomas. Samples were obtained from the Norwegian Radium Hospital and from the Helsinki University Central Hospital. Patients were 21-77 years (average of 41 years). Adjacent testicular tissue was available for 7 of 9 cases, and 2 samples were compared with 4 samples of testicular DNA used in the matched sets.

G. Loss of spots from RLGS profiles is due to methylation

In comparing RLGS profiles of DNAs from different tumors with control, healthy tissue DNAs, loss of a fragment or spot from an RLGS profile (Fig. 1A) was frequently detected. Loss of such a spot could be due to either methylation of DNA sequences at the NotI site giving rise to that spot, or to deletion of DNA surrounding that NotI site from the genome of the tumor. The relative contribution of each mechanism was assessed by using clones from the NotI/EcoRV genomic library, specific for lost spots, as probes in Southern blotting studies. In Fig. 2A, a section of an RLGS profile, from normal, healthy tissue was compared with tumor tissue from two gliomas, J7 and J16. This RLGS section contains spot 3C1. In tumor J16, spot 3C1 is absent from the RLGS profile. If there was a deletion of DNA surrounding the NotI site, however, the expected result in the Southern blot would be either no hybridization of the probe to the J16 genomic DNA or hybridization to a band of a size different from those detected in the lane containing normal, healthy tissue DNA digested with NotI plus EcoRV, and tumor tissue DNA digested with EcoRV alone. This result is not seen. These results show, therefore, that DNA corresponding to a missing 3C1 spot in J16 glioma DNA is present in the genome, as shown by the Southern hybridization result.

Likewise, DNA corresponding to specific RLGS spots missing in certain leukemias (Fig. 2B) and neuroectodermal tumors of childhood (Fig. 2C) are found to be present when these DNA are analyzed by Southern blotting. Overall, in 26 tumors where specific spots in RLGS profiles were missing DNA corresponding to the spot, was found to be present in the genome by Southern blotting. These results show that loss of spots on RLGS profiles is due to methylation of the corresponding NotI site and not deletion from the genome of DNA representing that spot. Therefore, methylation is the predominant mechanism underlying loss of spots from RLGS profiles.

H. Heterogeneity in CpG-island methylation across tumors.

To compare the overall pattern of methylated CpG islands among different tumors of the same tumor type, 1,184 spots in each of 98 tumors (and their non-tumorigenic controls) were analyzed by RLGS. The analysis was performed by determining the number of RLGS spots lost, or of decreased intensity, as compared to the controls. Each lost spot or spot of decreased

intensity is equivalent to one methylated CpG island. For each tumor type, the number of methylated CpG islands in each individual tumor, as compared to controls, was plotted (Fig. 3). These data showed that breast, head and neck, and testicular tumors had relatively low levels of methylation, with many such tumors showing no methylation. Colon tumors, gliomas, acute myeloid leukemias and primitive neuroectodermal tumors (PNETs) had a much higher frequency of methylation. Nonparametric comparison (Kruskal-Wallis procedure) of the methylation frequencies of the various tumor types showed significant differences between them (χ_6^2=56.9, P<0.0001).

Within a tumor type, the range of methylated CpG islands in individual tumors was variable. The data (Fig. 3) are not consistent with chance variation between tumors because, in the absence of heterogeneity, the variance of the methylation frequency would not be expected to be greater than the mean[1]. A formal test of this overdispersion was performed for each tumor type and the results are shown in Fig. 3 as a superimposition of the expected Poisson distribution on the dot plots. These data showed that aberrant methylation of CpG islands can be quantitatively different in individual tumors within a tumor type and more pronounced overall in particular tumor types.

I. Subsets of CpG islands were preferentially methylated in tumors

Through analysis of the RLGS spots lost in different tumors, it was determined that certain spots on the RLGS gels were lost in multiple tumors. This means that specific CpG dinucleotides were methylated in more than one tumor. This is shown in Fig. 4 where the number of tumors within a specific tumor type that had a particular CpG island methylated are shown.

To test the hypothesis that methylation of these common CpG islands was not random, a standard goodness-of-fit test was used.[2] This can be seen in the plots of Fig. 4 where the black

[1]Heterogeneity of methylation frequencies across samples was assessed within each tumor type by a standard test for evidence that the variance in methylation frequency exceeds the mean. This test is motivated by the Poisson approximation, which applies even if the frequencies of methylation vary across CpG islands. Moreover, a simple result from the binomial distribution shows that the test is conservative, because under homogeneity the population variance cannot exceed the mean.

[2]Under the null hypothesis of equal methylation frequencies for each CpG island, a goodness-of-fit test (χ^2) was applied to the observed versus expected frequencies of islands exhibiting

line of each plot shows the expected distributions if methylation of specific CpG islands in multiple tumors was random. It can be seen from Fig. 4 that for breast tumors, colon tumors, gliomas, acute myeloid leukemias and childhood PNETs, the actual distributions were significantly different ($P<0.0001$) from the theoretical distributions indicative of randomness. Similarly, the results for head and neck tumors were significant ($P<0.025$). The results for testicular tumors ($P=0.365$) were not significant. However, tumors of this type have a low overall methylation frequency and larger sample sizes are needed. Overall, the data indicate that the patterns of CpG island methylation in tumors is not random.

J. Frequencies of aberrant CpG-island methylation of shared and tumor-type-specific targets

Because the data have shown that they are methylated in a nonrandom fashion, CpG islands that are methylated at a high frequency in one or more tumor types can be used for diagnosis of tumors. From analysis of 98 tumors using NotI/EcoRV RLGS analysis, a number of spots that are absent or of decreased intensity, as compared to control healthy tissue DNA, have been found. Table I lists these spots. Each fragment (CpG island) is identified in three ways in the table. First, the location of each CpG island is designated as the distance (in cm) migrated during electrophoresis, from the gel origin, in both the first dimension and the second dimension. Second, each CpG island is given a three-variable designation (Y coordinate, X coordinate, fragment number). The X coordinate indicates horizontal direction on the two-dimensional RLGS profile and is a letter from B-G. The Y coordinate indicates vertical direction and is a number from 1-5. Together, an X and Y designation divide the RLGS profile into 28 sections. Within each section, the spots/fragments are given a number. Such a profile is available at: http://pandora.med.ohio-state.edu/masterRLGS/. Third, the partial DNA sequence of individual spots has been determined by sequencing of library clones corresponding to each spot. These sequences are shown in the attached Sequence Listing and have been assigned SEQ ID NOS. from 1 to 82.

The diagnostic NotI/EcoRV spots are of two types (Fig. 1). The first type of spot is absent or of decreased intensity in a single tumor type. For example, the NotI site that is part of the CpG island designated 2.B.53, is methylated only in head and neck tumors. Similarly, the NotI site of CpG island 2.F.2 is methylated only in breast tumors.

---

methylation in multiple tumors within each tumor type.

The second type of spot is absent or of decreased intensity in more than one type of tumor. For example, the NotI/EcoRV spot designated 2.C.24 is missing in gliomas and AMLs. Similarly, the NotI/EcoRV spot designated 3.B.55 is methylated in breast, colon and PNETs.

Table I. Diagnostic CpG islands in tumors.

CpG Island[1]	1st-D (cm)[2]	2nd-D (cm)[2]	Type[3]	Methylated In[4]:
2.B.53	36.85	9.25	t	HN
2.C.24	30.3	5.32	s	Abt/Leu
2.C.29	27.8	5.45	s	Leu/Hn
2.C.35	29.45	6.9	s	Abt/Bre/Cln/Leu/Pbt
2.C.54	32.38	9.42	s	Leu/Hn
2.C.57	30.9	8.5	ND	Tst
2.C.58	31.2	9.2	s	Abt/Leu
2.C.59	30.4	9.35	ND	Hn
2.D.10	27.55	5.3	s	Leu/Pbt
2.D.14	24.25	4.47	t	Leu
2.D.20	26.3	5.3	t	Cln
2.D.25	27.15	6.4	ND	Bre
2.D.27	25.65	5.82	ND	Hn
2.D.34	23.62	6.6	s	Leu/Pbt
2.D.40	23.95	7.25	ND	Pbt
2.D.48	26.1	8.1	ND	Leu
2.D.55	24.2	8.3	s	Cln/Leu
2.D.74	23.95	9.35	s	Abt/Bre/Cln/Leu
2.E.20	20.6	5.95	ND	Pbt
2.E.24	19.35	5.7	s	Abt/Leu
2.E.25	18.27	5.65	t	Bre
2.E.30	20.35	6.4	s	Abt/Bre/Leu
2.E.37	21.42	7.1	ND	Bre
2.E.4	21.1	4.48	s	Leu/Pbt
2.E.40	NA	NA	ND	Tst
2.E.61	19.4	8.08	s	Abt/Pbt
2.E.64	20.5	8.35	s	Abt/Cln
2.F.2	17.27	4.72	t	Bre
2.F.41	NA	NA	t	Tst
2.F.50	15.23	7	s	Abt/Leu
2.F.59	17.49	8	ND	Bre
2.F.70	15.88	13.3	s	Pbt/Tst
2.G.10	10.29	4.49	s	Leu/Tst
2.G.108	7.68	7.44	ND	Bre
3.B.30	35.4	12.55	ND	Tst

3.B.36	34.2	11.8	s	Abt/Cln/Leu/Pbt
3.B.55	NA	NA	s	Bre/Cln/Pbt
3.C.01	31.6	9.7	s	Abt/Cln/Leu
3.C.16	27.9	11.8	t	Pbt
3.C.17	29.2	10.57	t	Cln
3.C.30	31.61	10.37	t	Bre
3.C.35	31.6	11.5	t	Pbt
3.C.64	29.1	14.05	ND	Bre
3.D.21	24.2	10.75	t	Leu
3.D.24	23.2	11.03	s	Abt/Leu
3.D.35	26.1	11.65	s	Abt/Cln/Leu/Pbt
3.D.40	23.4	12.26	s	Abt/Cln/Leu
3.D.44	24.45	12.82	t	Leu
3.D.60	27.2	12.4	s	Abt/Cln/Leu
3.E.04	20.4	14.2	s	Hn/Pbt
3.E.50	20.55	10.7	s	Hn/Tst
3.E.55	18.78	10.55	s	Cln/Leu
3.E.57	18.09	10.9	s	Cln/Hn
3.E.59	18.4	9.72	s	Abt/Tst
3.F.16	16.6	9.75	ND	Leu
3.F.2	16.73	9.35	s	Leu/Tst
3.F.50	16.25	11.6	s	Cln/Leu/Tst
3.F.72	16.9	13.7	t	Leu
3.F.82	13.8	13.12	s	Abt/Cln/Leu
3.G.46	9.88	11.5	ND	Bre
3.G.78	10	12.93	ND	Leu/Pbt
4.B.44	33.7	18.53	s	Cln/Hn
4.B.56	33.2	19.45	s	Bre/Leu
4.C.05	30	14.9	ND	Bre
4.C.25	28.62	17	ND	Bre
4.C.42	NA	NA	ND	Tst
4.C.9	30.3	15.3	ND	Bre
4.D.07	22.9	14.5	s	Leu/Tst
4.D.08	23.5	15	s	Abt/Tst
4.D.12	25	14.85	s	Abt/Leu/Tst
4.D.13	24.95	15.3	s	Abt/Bre
4.D.47	27.6	18.25	s	Abt/Leu/Pbt
4.E.53	19.39	18.43	t	Leu
4.F.15	13.25	15.45	t	Cln
4.F.17	14.1	15.6	s	Abt/Bre/Cln
4.F.22	17.56	16.2	s	Cln/Hn/Leu
4.F.6	14.85	14.59	ND	Bre
4.F.69	12.58	18.86	t	Abt
5.D.9	25.17	23.4	t	Hn

5.E.2	20.58	19.5	t	Bre
5.E.25	18.7	21.3	t	Cln
5.E.4	18.45	19.75	s	Abt/Bre/Leu
[1]Y coordinate, X coordinate, fragment number				
[2]NA, spots too close to analyze.				
[3]T, tumor-type specific target of methyaltion; s, shared target of methylation; ND, not determined.				
[4]Types of tumor in which CpG island is methylated: Abt, gliomas; Bre, breast; Cln, colon; Hn, head and neck; Leu, acute myeloid leukemia; Pbt, pediatric brain tumors; Tst, testicular germ cell tumors.				

Example 2. Identification of diagnostic markers for lung cancer using AscI and RLGS

Tissue from lung tumors was obtained as surgical tissue samples. Where possible, surrounding non-tumor tissue from the same patient was obtained and used as a control. DNA was isolated from the tissue as described in Example 1. In preparation for RLGS analysis, the ends of the DNA were blocked as described in Example 1. The DNA was then digested with AscI followed by digestion with EcoRV. The AscI restriction enzyme recognizes the sequence 5'GGCGCGCC3' and does not cleave said sequence if cytosines within the sequence are methylated. First dimension gel electrophoresis, in-gel digestion with HinfI, second dimension gel electrophoresis and autoradiography were performed as described in Example 1.

RLGS profiles from lung tumor DNA were compared with RLGS profiles obtained from healthy, non-tumor tissue DNA. Spots which were lost or present at reduced intensity in tumor tissue RLGS profiles as compared to profiles obtained from healthy tissue were noted. Eight spots were lost or altered in the RLGS profiles from multiple lung tumor samples. A compilation of such spots is shown in Table II (lung tumors).

DNA sequence information was obtained from the lung cancer-specific spots. This was done by sequencing individual clones of an AscI/EcoRV library that was made from DNA from healthy tissue. Individual clones of this library that corresponded to spots on the AscI/EcoRV RLGS profile were identified by overloading an RLGS gel with DNA from various groups of library clones, as was described earlier in the specification of this application for the NotI/EcoRV library. After individual clones were matched with spots in the AscI/EcoRV profile, the DNA from the spots that were missing in profiles from the lung tumor DNAs were sequenced. Such sequence information is shown in the attached DNA Sequence Listing.

Table II. Diagnostic CpG islands grouped by tumor type.

Library	Tumor type	Tumor type specific (+), shared (-), or not determined (ND)[1]	CpG island designation`
NotI/EcoRV	Breast	+	2.E.25, 2.F.2, 3.C.30, 5.E.2
		-	3.B.55, 4.B.56, 4.D.13, 4.F.17, 2.D.74, 2.C.35, 2.E.30, 5.E.4
		ND	2.D.25, 2.E.37, 2.F.59, 2.G.108, 3.C.64, 3.G.46, 4.C.05, 4.C.25, 4.C.9, 4.F.6
NotI/EcoRV	Colon	+	2.D.20, 3.C.17, 4.F.15, 5.E.25
		-	3.E.57, 4.B.44, 4.F.22, 2.D.55, 3.E.55, 3.F.50, 3.B.55, 4.F.17, 2.D.74, 2.C.35, 2.E.64, 3.C.01, 3.D.40, 3.D.60, 3.F.82, 3.B.36, 3.D.35
		ND	---
NotI/EcoRV	Glioma	+	4.F.69
		-	4.D.13, 4.F.17, 2.D.74, 2.C.35, 2.E.30, 5.E.4, 2.E.64, 3.C.01, 3.D.40, 3.D.60, 3.F.82, 3.B.36, 3.D.35, 2.C.24, 2.C.58, 2.E.24, 2.F.50, 3.D.24, 4.D.47, 4.D.12, 2.E.61, 3.E.59, 4.D.08
		ND	---
NotI/EcoRV	Head & neck	+	2.B.53, 5.D.9
		-	2.C.29, 2.C.54, 3.E.04, 3.E.50, 3.E.57, 4.B.44, 4.F.22
		ND	2.C.59, 2.D.27
NotI/EcoRV	Acute myelogenous Leukemia	+	2.D.14, 3.D.21, 3.D.44, 3.F.72, 4.E.53, 2.C.29, 2.C.54

		-	2.D.10, 2.D.34, 2.E.4, 2.G.10, 3.F.2, 4.D.07, 4.F.22, 2.D.55, 3.E.55, 3.F.50, 2.E.64, 3.C.01, 3.D.40, 3.D.60, 3.F.82, 3.B.36, 3.D.35, 3.C.01, 3.D.40, 3.D.60, 3.F.82, 3.B.36, 3.D.35, 2.C.24, 2.C.58, 2.E.24, 2.F.50, 3.D.24, 4.D.47, 4.D.12
		ND	2.D.48, 3.F.16, 3.G.78, 4.B.56
NotI/EcoRV	Pediatric neuroectodermal tumor of childhood	+	3.C.16, 3.C.35, 3.E.04
		-	2.D.10, 2.D.34, 2.E.4, 3.B.55, 2.C.35, 3.B.36, 3.D.35, 4.D.47, 2.E.61
		ND	2.D.40, 2.E.20, 3.G.78
NotI/EcoRV	Testicular	+	2.F.41
		-	2.G.10, 3.F.2, 4.D.07, 3.E.50, 3.F.50, 4.D.12, 3.E.59, 4.D.08
		ND	2.C.57, 2.E.40, 3.B.30, 4.C.42
AscI/EcoRV	Lung	+	
		-	
		ND	A.2.F.45, A.2.F.50, A.2.F.67, A.3.F.38, A.4.D.30, A.4.D.36, A.4.E.32, A.5.E.28[2]

[1]ND, not determined. Indicates that the designated CpG island was methylated in the indicated tumor type but its methylation in other tumor types was not determined.
[2]The "A" preceding the X, Y, number designation for the CpG islands indicates that these islands are from the AscI/EcoRV RLGS profile.

Example 3. Design of primers for cancer diagnosis

Primers are designed for diagnosis of cancer using methylation-specific PCR (MSR). The primers are designed to amplify regions of the human genome whose sequences are contained within the library clones disclosed in this application. Two sets of primers are needed for each library clone whose DNA sequence is to be used for diagnosis of cancer. Each primer

set is designed to amplify the same region of the genome, said region beginning at the end of a library clone containing the methylation-sensitive restriction enzyme recognition site (i.e., the NotI site for the library described in Example 1; the AscI site for the library described in Example 2) and ending at a region contained within the clone up to 200 nucleotides from the methylation-sensitive restriction enzyme recognition site.

The first set of primers is designed to amplify template genome DNA whose cytosine residues are not methylated and, after bisulfite treatment, the cytosines of said genome DNA are converted to uracil. The second set of primers is designed to amplify template genome DNA which is methylated on cytosines that comprise CpG dinucleotides. Such methylated cytosines are unaffected by bisulfite treatment. Therefore, by using two sets of primers, one set that will amplify only unmethylated DNA and another set that will amplify only methylated DNA, methylation state of the template DNA can be determined. Such methylation state can be diagnostic for cancer.

The primers used for MSR are designed to be from 15 to 34 nucleotides in length and contain within their sequence either CpG dinucleotides or dinucleotides complementary to CpG dinucleotides that have been treated with bisulfite. It is preferred that the 3' ends of primers used to amplify unmethylated DNA are CpA dinucleotides. It is preferred that the 3' ends of primers used to amplify methylated DNA are CpG dinucleotides.

For each library clone to be used diagnostically, the first set of primers are designed to amplify genome DNA that is not methylated. After treatment of such genome DNA with bisulfite, all such unmethylated cytosines are converted to uracil. PCR primers that will use such DNA as a template and amplify it, will have adenine residues which are complimentary to these uracils.

For the first set of primers, the 5' end of one of the primers begins at the end of the library clone containing the methylation-sensitive restriction enzyme recognition site. The sequence of this primer is identical in sequence to the strand of the template which has its 5' end as part of the methylation-sensitive restriction enzyme site, except that guanine residues are replaced with adenine residues. The adenines allow the primer to hybridize with the template strand in which cytosines have been converted to uracils by bisulfite. This primer extends to a length of between 15 and 32 total nucleotides. Preferably, the 3' end of said primer ends with a

CpA dinucleotide, the adenine of said dinucleotide hybridizing to a uracil which, before bisulfite treatment, had been a cytosine that comprised a CpG dinucleotide.

The diagram below shows implementation of these rules to select a primer that can be used to amplify clone 2.B.53 of the NotI/EcoRV library (Table I and attached sequence listing). In the diagram, I shows the end of the 2.B.53 clone containing the methylation-sensitive NotI site (NotI recognition sequence is shown in bold letters). CpG dinucleotides are shaded. To amplify a region of this clone rightward of the NotI site, the first primer is identical to the top strand of the duplex shown in I. However, since bisulfite treatment of the DNA in I converts cytosines to uracils, guanines within the PCR primer must be replaced with adenines. II shows the sequence of the bottom strand of I after bisulfite treatment converts cytosines to uracils. A primer complementary to the bisulfite-treated bottom strand has the sequence shown in III.

I

5'GCGGCCGCGGGTTAGCTTCTCCTGTCCGAACGCAGGG-----

3'CGGCCGGCGCCAATCGAAGAGGACAGGCTTGCGTCCC-----

II

3'UGUUGGUGUUAATUGAAGAGGAUAGGUTTGUGTUUU-----

III

5'ACAACCACAATTAACTTCTCCTATCCAAACA 3'

III shows the entire sequence of one of the two primers used to amplify unmethylated genome DNA corresponding to library clone 2.B.53. This primer encompasses 5 CpG dinuceotides, as shown by the shading in I above. Encompassment of 2 or more such CpG dinucleotides is preferred so that this primer will not hybridize to a bisulfite-treated template which contains methylated cytosines. The 3'end of the primer shown in III ends in a CpA dinucleotide. This is also preferred in order to provide maximal discrimination of the primer between methylated and unmethylated template DNA in MSR. The primer shown in III has a length of 31 nucleotides.

The second primer is designed to work with the first primer in PCR amplification such that a fragment of less than about 200 base pairs is amplified. Therefore, this primer is made to a sequence rightward of the sequence shown in I. The sequence of this primer is complementary in sequence to the strand of the template which has its 5' end as part of the methylation-sensitive

restriction enzyme site, except that guanine residues are replaced with adenine residues. This primer is preferably between 15 and 32 nucleotides in length. This primer is also designed to preferably encompass 2 or more CpG dinucleotides. Preferably, the 3' end of said primer ends with a CpA dinucleotide.

The diagram below shows implementation of these rules to select a primer that can be used to amplify unmethylated genome DNA corresponding to clone 2.B.53 of the NotI/EcoRV library. IV shows a region of the 2.B.53 clone about 70 nucleotides rightward of the sequence in I of the earlier diagram. The CpG dinucleotides within the sequence are shaded. To amplify a region leftward of this region, this second primer must be complementary to the top strand of the duplex shown in IV. However, bisulfite treatment of the DNA in IV converts cytosines to uracils. A primer complementary to this bisulfite-treated top strand has the sequence shown in VI.

IV

```
5'-----GGAGTCGCGCGTCGCGCGGAGGCTGCGCCGCGCCACCGA-----3'
3'-----CCTCAGCGCGCAGCGCGCCTCCGACGCGCGCGCGTGGCT-----5'
```

V

```
5'-----GGAGTUGUGGTUGUGGGAGGUTGUGUUGUGUAUUGA-----3'
```

VI

```
3' ACACCAACACCCTCCAACACAACACATAACT 5'
```

VI shows the entire sequence of the second primer used to amplify unmethylated genome DNA corresponding to library clone 2.B.53. This primer encompasses 8 CpG dinucleotides, as shown by the shading in IV. Encompassment of 2 or more such CpG dinucleotides is preferred. The 3'end of the primer shown in VI ends in a CpA dinucleotide. This is also preferred. The primer shown in VI has a length of 31 nucleotides. Together, the first and second primers amplify a PCR fragment of 128 base pairs in length.

The above primers amplify genome DNA that does not contain 5-methylcytosine. The above primers will not amplify genome DNA containing 5-methylcytosines because 5-methylcytosines are not converted to uracils by bisulfite treatement. The two primers already described (III and VI), therefore, will not be complementary to bisulfite-treated genome DNA which is methylated.

Therefore, a second set of primers is designed to amplify genome DNA that is methylated. Methylation in human cells occurs at cytosines that are part of CpG residues. Such methylated cytosines are not converted to uracil by bisulfite treatment. Cytosines that are not part of CpG residues are not methylated and, therefore, are converted to uracil by bisulfite. The primers of the second set are designed to amplify the same region of a library clone as did the first set of primers. But, because the genome DNA contains both cytosines that are methylated and cytosines that are not methylated, the sequences of primers used to amplify such DNA are different than the sequences of the first primer set. Like the first set of primers, however, the primers of the second set are preferably between 15 and 32 nucleotides in length. Preferably the 3' ends of such primers contain CpG dinucleotides.

The diagram below shows implementation of these rules to select the first of two primers that can be used to amplify methylated genomic DNA corresponding to clone 2.B.53 of the NotI/EcoRV library. In the diagram below, VII shows the end of the 2.B.53 clone containing the NotI site (NotI recognition sequence is bolded). CpG dinucleotides are shaded. Cytosines within said CpG dinucleotides are methylated and are underlined in VII to indicate methylation to 5-methylcytosine. Treatment of the DNA in VII with bisulfite produces a bottom strand with the sequence shown in VIII. In VIII, only unmethylated cytosines are converted to uracil by bisulfite.

VII

5'GCGGCCGCGGTTAGCTTCTCCTGTCCGAACGCAGGG-----

3'CGCCGGCGCCAATCGAAGAGGACAGGCTTGCGTCCC-----

VIII

3'UGCUGGCGCUAATUGAAGAGGAUAGGCTTGCGTUUU-----

IX

5'ACGACCGCGATTAACTTCTCCTATCCGAACG 3'

A primer complementary to the bisulfite-treated bottom strand shown in VIII is shown in IX. Said primer will prime PCR amplification of sequences rightward of those shown in VII. The primer shown in IX encompasses 5 CpG dinucleotides. Encompassment of 2 or more such CpG dinucleotides is preferred. The 3' end of the primer shown in IX ends in CpG. This is also preferred. The primer shown in IX has a length of 31 nucleotides.

A second primer is designed to work with the primer shown in IX to amplify methylated genome template DNA. Design of such a primer is shown below. In the diagram, X shows the same region of clone 2.B.53 (approximately 70 nucleotides rightward of the sequences shown in VII) that is shown in IV. Treatment of the DNA in X with bisulfite produces a top strand with the sequence shown in XI. In XI, only unmethylated cytosines are converted to uracil by bisulfite.

X

5′-----GGAGTCGCGGTCGCGGGAGGCTGCGCCGCGCACCGA-----3′

3′-----CCTCAGCGCCAGCGCCCTCCGACGCGGCGCGTGGCT-----5′

XI

5′-----GGAGTCGCGGTCGCGGGAGGUTGCGUCGCGUAUCGA-----3′

XII

3′ GCGCCAGCGCCCTCCAACGCAGCGCATAGCT 5′

A primer complementary to the bisulfite-treated top strand (XI) has the sequence shown in XII. Said primer will prime PCR amplification of sequences leftward of those shown in X. The primer shown in XII encompasses 8 CpG dinucleotides. Encompassment of 2 or more such CpG dinucleotides is preferred. The 3' end of the primer shown in XII ends in a CpG dinucleotide. This is also preferred. The primer shown in XII has a length of 31 nucleotides. Together, the first (IX) and second primers (XII) of the second set amplify a PCR fragment of 128 base pairs in length.

Example 4. Use of oligonucleotides to diagnose cancer

The library clones, and DNA sequences within, can be used to detect DNA methylation in a genome at the specific sequences identified by the sequences within the clone. Such detection can be diagnostic for cancer. Various methods can be used for such diagnosis.

A. Diagnosis of cancer using methylation-sensitive restriction enzymes followed by Southern blot

Cleavage or lack of cleavage by a methylation-sensitive restriction enzyme at a specific restriction enzyme recognition site can be detected by a probe for the specific recognition site,

using Southern blotting. Genomic DNAs were isolated (as described in Example 1) from tumor tissue from a patient with acute myelogenous leukemia (AML). Cells from the same patient after chemotherapy and remission of the disease served as a source of control, healthy tissue DNA. The AML and control DNAs were designated as 26T and 26N, respectively. The DNAs were digested with NotI and EcoRV for 4 hours and then electrophoresed through a 0.8% agarose gel. DNA within the gel was depurinated by soaking the gel in 0.2 N HCl for 10 min. The gel was equlibrated in transfer solution (0.5 N NaOH, 1 M NaCl) for 10 min. and then blotted to Zeta Bind-GT nylon membranes (Bio-Rad). Blots were crosslinked with UV light, baked in a vacuum oven and then prehybridized for 1 hour at 65°C in a solution of 7% SDS, 500 mM sodium phosphate buffer (pH 7.2) and 1 mM EDTA. The blot was hybridized overnight at 65°C in prehybridization solution with 10 ng of α-^{32}P-labeled probe at a specific activity of 10^8-10^9 dpm/µg. The DNA probe used was the 2.C.40 clone from the NotI/EcoRV 2.C.40library. The purified NotI/EcoRV fragment (50 ng) was labeled with [α-^{32}P]dCTP by random priming using the Prime-It II random-prime labeling kit (Stratagene). The blot was washed with two quick rinses at 65°C in wash solution 1 (100 mM sodium phosphate buffer, pH 7.2, 0.1% SDS), followed by one 30 min. wash at 65°C in wash solution 1. The blot was next washed for 30 min. at 65°C in wash solution 2 (40 mM sodium phosphate buffer, pH 7.2, 0.1% SDS). Bands were visualized by autoradiography using Kodak X-OMAT AR film.

Fig. 2B shows the data. The first 2 lanes of the autoradiograph are relevant. The first lane, labeled 26N is the normal, healthy tissue DNA cleaved with both NotI and EcoRV. The 26N lane shows a band near the bottom of the autoradiograph labeled "NotI/EcoRV." This is fragment resulting when the NotI site present in the 2.C.40 clone is unmethylated. The adjacent lane, labeled "26T," is the tumor tissue DNA cleaved with both NotI and EcoRV. It is seen that this band, labeled "EcoRV," does not migrate as fast as did the 26N band. The reason is that the NotI site present in the 2.C.40 clone is methylated and the NotI enzyme was unable to cleave at this site.

B. Diagnosis of cancer using methylation-specific PCR (MSR)

MSR is a technique whereby DNA is amplified by PCR dependent upon the methylation state of the DNA. In this example, the specific areas of the genome whose methylation status is to be determined are the regions at the ends of the CpG islands that are demarcated by the

methylation-sensitive restriction enzyme recognition sequence. In the case of the NotI/EcoRV RLGS profiles, this is the NotI site. In the case of the AscI/EcoRV RLGS profiles, this is the AscI site, at the end of each clone.

For the purposes of this example, the methylation status of genomic sequences corresponding to the NotI site of clone 2.B.53 of the NotI/EcoRV library is examined. Genomic DNA is first isolated from normal tissue and from tumor tissue, as described in Example 1. This DNA is then treated with bisulfite. This is done by taking 1 μg of genomic DNA in a volume of 50 μl and denaturing said DNA in a final concentration of 0.2 M NaOH. Thirty microliters of 10 mM hydroquinone and 520 μl of 3 M sodium bisulfite, at pH 5.0, are added, mixed and incubated under mineral oil at 50°C for 16 hours. The modified DNA is then purified using the Wizard DNA purification resin (Promega) and eluted into 50 μl of water. Modification is completed by NaOH (final concentration, 0.3 M) treatment for 5 min. at room temperature, followed by ethanol precipitation. DNA is resuspended in water.

Each genomic DNA is then used in two PCR reactions. One PCR reaction will amplify DNA that is not methylated and has, therefore, been modified by bisulfite. The second PCR reaction will amplify DNA that is methylated. Separate primers are used for each reaction. To determine the methylation status of the NotI site in the genomic DNA which corresponds to the 2.B.53 clone, the two sets of primers described in Example 3 are used. Each PCR reaction contains 1X PCR buffer (16.6 mM ammonium sulfate, 67 mM Tris, pH 8.8, 6.7 mM $MgCl_2$, 10 mM 2-mercaptoethanol), dNTPs (each at 1.25 mM), primers (300 ng each per reaction), and 50 ng bisulfite-modified DNA in a final volume of 50 μl. Separate control reactions are run which contain DNA that has not been modified by bisulfite. Reactions are hot-started at 95°C for 5 min. before the addition of 1.25 units of *Taq* polymerase. Amplification is carried out for 35 cycles (30 sec at 95°C, 30 sec at the annealing temperature, and 30 sec at 72°C), followed by a final 4 min. extension at 72°C. Each PCR reaction is directly loaded onto nondenaturing 6-8% polyacrylamide gels and electrophoresed. Gels are stained with ethidium bromide and visualized under UV illumination.

If input genomic DNA is not methylated at cytosines within CpG dinuceotides at the NotI site corresponding to the end of the 2.B.53 CpG island clone, the PCR reaction using the primers specific for nonmethylated DNA (primers III and VI in Example 3) will produce an amplification product of 128 base pairs in length. Using the same input genomic DNA, the PCR reaction using

the primers specific for methylated DNA (primers IX and XII in Example 3) will not produce an amplification product.

If input genomic DNA is methylated at cytosines within CpG dinucleotides at the NotI site corresponding to the end of the 2.B.53 CpG island clone, the PCR reaction using the nonmethylation-specific primers will not produce an amplification product. Using the same input genomic DNA, the PCR reaction using the methylation-specific primers will produce an amplification product of 128 base pairs in length.

Example 5. Detection of gene expression

The library clones (Tables I and II) and DNA sequences (attached sequence listing) are useful for determining whether genes encoded within said clones are being transcribed in tumor tissue or cultured cells. To determine transcription, RNA was isolated from five different human glioma cell lines (U87MG, U178, T98G, U251 and LN235) using Trizol (Gibco BRL). Such RNA isolation reagent is known to those skilled in the art. RNAs were quantified using a spectrophotometer and then treated with amplification grade Dnase I (Gibco). The RNA (2 μg) was reverse transcribed by incubation with oligo-dT and random primers in a 20 μl reaction, heated to 70°C for 10 min. and placed on ice. A mix containing 1X reaction buffer (Gibco), DTT (10 mM), dNTPs (0.5 mM each), and RNAsin (80 U, Promega) was added to each sample. The samples were divided into two tubes, each containing 19 μl, and incubated at 37°C for 2 min. M-MLV reverse transcriptase (RT, 200 U) was added to one of the two tubes and each was incubated at 37°C for 1 h. DEPC-treated water (30 μl) was added to each sample and heated in boiling water for 5 min.

PCR amplification of the reverse transcribed RNA was then performed. In this study, transcripts encoded by sequences within the 2.C.24 library clone (Table I) were looked for. A computer search using the BLAST program had identified an open reading frame within the sequence of this library clone. PCR primers were made to this region. Primer 1 was 5' TGGTGCTGAAGTCGGTGAA 3'. Primer 2 was 5' GGGCCATCTTCACCATCTG 3'.

These primers (10 pmol of each) were used in 10 μl PCR reactions which contained 1.5 μl of the reverse transcription reaction, 1X reaction buffer, Taq polymerase (0.5 U, Boehringer),

and dNTPs (250 μM each). For each gene, separate amplification reactions were carried out using RT-positive and RT-negative reactions as template. Amplification was not detected from the RT-negative reactions. The PCR reactions were carried out by heating the samples to 94°C for 5 min and then amplifying for 35 cycles, each cycle consisting of 94°C for 30 sec., a 30 sec. annealing step at 56°C, and 72°C for 45 sec. The reactions were then incubated at 72°C for 7 min and cooled to 4. The sample was then electrophoresed through an agarose gel containing ethidium bromide and PCR products were visualized using an Eagle Eye gel documentation system (Stratagene). The correct identity of the PCR products was confirmed by nucleotide sequencing of both strands.

The data showed that no transcripts encoded by this region of the 2.C.24 clone were found in any of the 5 glioma cell lines. Such expressed transcripts are present in RNA obtained from human fetal brain and adult brain.

In addition to examination of cell lines, tumor tissue obtained from patient samples can be similarly tested for the presence of transcripts by one skilled in the art. Other techniques to detect transcripts can also be used. Such techniques include, for example, Northern blot hybridization, RNase protection and primer extension assays.

CLAIMS

What is claimed is:

1. A method of identifying CpG islands which are preferentially methylated in malignant cells contained within a tumor or neoplasm, comprising:

a) digesting genomic DNA obtained from the malignant cells with an infrequently-cutting, methylation-sensitive, restriction enzyme to provide a set of malignant cell restriction fragments;

b) digesting genomic DNA obtained from non-malignant, control cells with an infrequently-cutting, methylation-sensitive, restriction enzyme to provide a set of control cell restriction fragments;

c) attaching a detectable label to the ends of the malignant cell restriction fragments and the control restriction fragments;

d) digesting the labeled malignant cell and control cell restriction fragments with a second restriction enzyme;

e) separating the labeled malignant cell restriction fragments and the labeled control cell restriction fragments, wherein the malignant cell restriction fragments and the control cell restriction fragments are separated by electrophoresis on two different gels;

f) digesting the restriction fragments in each of said gels with a third restriction enzyme;

g) electrophoresing the restriction fragments in each of said gels in a direction perpendicular to the first direction to provide a first pattern of detectable malignant cell restriction fragments and a second pattern of detectable control cell restriction fragments; and

h) comparing the first pattern to the second pattern to identify diagnostic control cell restriction fragments in said second pattern which are absent or exhibit a decreased intensity in the first pattern, wherein said diagnostic control cell restriction fragments comprise a CpG island that is unmethylated in the DNA of the control cells and methylated in the DNA of the malignant cells.

2. The method of claim 1 further comprising the step of determining the sequence of at least a portion of a diagnostic control cell restriction fragment, wherein said portion is located at or near an end of the fragment .

3. The method of claim 1 further comprising the step of obtaining a clone from a DNA

library which comprises a diagnostic control cell restriction fragment.

4. A method of preparing a polynucleotide or oligonucleotide for characterizing tissue obtained from a subject suspected of having cancer, comprising:

synthesizing a polynucleotide or oligonucleotide which comprises a sequence which is identical to or substantially complementary to a target sequence on one of the strands of a diagnostic control fragment identified according to the method of claim 2, wherein said target sequence comprises at least two CpG dinucleotides, wherein said oligonucleotide is from 15 to 34 nucleotides in length, and wherein said polynucleotide is from 35 to 2000 nucleotides in length.

5. The method of claim 4 wherein said target sequence is located at or near the control restriction fragment end which was cleaved by the methylation-sensitive, restriction enzyme.

6. The method of claim 4 wherein the target sequence is located from about 100 nucleotides to about 500 nucleotides downstream of the control restriction fragment end that was cleaved by the methylation-sensitive, restriction enzyme.

7. The method of claim 4 wherein the control restriction fragment comprises a sequence selected from the group consisting of SEQ. ID. NO.:1, SEQ. ID. NO.:2, SEQ. ID. NO.:3, SEQ. ID. NO.:4, SEQ. ID. NO.:5, SEQ. ID. NO.:6, SEQ. ID. NO.:7, SEQ. ID. NO.:8, SEQ. ID. NO.:9, SEQ. ID. NO.:10, SEQ. ID. NO:11, SEQ. ID. NO.: 12, SEQ. ID. NO.:13, SEQ. ID. NO.:14, SEQ. ID. NO.:15, SEQ. ID. NO.: 16, SEQ. ID. NO.:17, SEQ. ID. NO.:18, SEQ. ID. NO.: 19, SEQ. ID. NO.:20, SEQ. ID. NO.:21, SEQ. ID. NO.:22, SEQ. ID. NO.:23, SEQ. ID. NO.:24, SEQ. ID. NO.:25, SEQ. ID. NO.:26, SEQ. ID. NO.:27, SEQ. ID. NO.:28, SEQ. ID. NO.:29, SEQ. ID. NO.:30, SEQ. ID. NO.:31, SEQ. ID. NO.:32, SEQ. ID. NO.:33, SEQ. ID. NO.:34, SEQ. ID. NO.:35, SEQ. ID. NO.:36, SEQ. ID. NO.:37, SEQ. ID. NO.:38, SEQ. ID. NO.:39, SEQ. ID. NO.:40, SEQ. ID. NO.:41, SEQ. ID. NO.:42, SEQ. ID. NO.:43, SEQ. ID. NO.:44, SEQ. ID. NO.:45, SEQ. ID. NO.:46, SEQ. ID. NO.:47, SEQ. ID. NO.:48, SEQ. ID. NO.:49, SEQ. ID. NO.:50, SEQ. ID. NO.:51, SEQ. ID. NO.:52, SEQ. ID. NO.:53, SEQ. ID. NO.:54, SEQ. ID. NO.:55, SEQ. ID. NO.:56, SEQ. ID. NO.:57, SEQ. ID. NO.:58, SEQ. ID. NO.:59, SEQ. ID. NO.:60, SEQ. ID. NO.:61, SEQ. ID. NO.:62, , SEQ. ID. NO.:63, SEQ. ID. NO.:64, SEQ. ID. NO.:65, SEQ. ID. NO.:66, SEQ. ID. NO.:67, SEQ. ID. NO.:68, SEQ. ID. NO.:69, SEQ. ID. NO.:70, SEQ. ID. NO.:71, SEQ. ID. NO.:72, SEQ. ID. NO.:73, SEQ. ID. NO.:74, SEQ. ID. NO.:75, SEQ. ID. NO.:76, SEQ. ID. NO.:77, SEQ. ID. NO.:78, SEQ. ID. NO.:79,

SEQ. ID. NO.:80, SEQ. ID. NO.:81, SEQ. ID. NO.:82, SEQ ID NO: 83, SEQ ID NO. 84, SEQ ID. NO. 85, SEQ. ID. NO. 86, SEQ. ID. NO. 87, SEQ. ID. NO. 88, SEQ. ID. NO. 89, SEQ. ID. NO. 90, SEQ. ID. NO. 91, SEQ ID. NO. 92, and SEQ. ID. NO. 93.

8. An isolated polynucleotide or oligonucleotide for characterizing cells that are obtained from a subject suspected of having a cancer which is associated with methylation of one or a plurality of CpG islands in the genomic DNA of malignant cells, wherein said polynucleotide or oligonucleotide comprises a sequence which is identical to or complementary to a target sequence on one of the strands of a diagnostic control fragment identified according to the method of claim 2, wherein said target sequence comprises at least two CpG dinucleotides, wherein said oligonucleotide is from 15 to 34 nucleotides in length; and wherein said polynucleotide is from 35 to 3000 nucleotides in length.

9. The isolated polynucleotide or oligonucleotide of claim 8 wherein said target sequence is located at or near the control restriction fragment end which was cleaved by the methylation sensitive restriction enzyme.

10. The isolated polynucleotide or oligonucleotide of claim 8 wherein the target sequence is located from about 100 nucleotides to about 500 nucleotides downstream of the control restriction fragment end that was cleaved by the methylation-sensitive, restriction enzyme.

11. An isolated polynucleotide or oligonucleotide for characterizing cells which are obtained from a subject suspected of having a cancer which is associated with methylation of one or a plurality of CpG islands in the genomic DNA of malignant cells, wherein said polynucleotide or oligonucleotide comprises a sequence which is identical to or complementary to a modified target sequence on one of the strands of a diagnostic control fragment identified according to the method of claim 2, wherein said modified target sequence is derived from a target sequence that has been modified by treatment with sodium bisulfite, wherein said modified target sequence lacks cytosines and comprises at least two UpG dinucleotides, wherein said oligonucleotide is from 15 to 34 nucleotides in length; and wherein said polynucleotide is from 35 to 3000 nucleotides in length.

12. The isolated polynucleotide or oligonucleotide of claim 11 wherein the modified target sequence is derived from a target sequence located at or near the control restriction fragment end that was cleaved by the methylation sensitive restriction enzyme.

13. The isolated polynucleotide or oligonucleotide of claim11 wherein the modifed target

sequence is derived from a target sequence that is located from about 100 nucleotides to about 500 nucleotides downstream of the control restriction fragment end that was cleaved by the methylation-sensitive restriction enzyme.

14. An isolated polynucleotide for characterizing cells which are obtained from a subject suspected of having a cancer selected from the group consisting of glioma, acute myeloid leukemia, primitive neuroectodermal tumors of childhood, breast cancer, colon cancer, head and neck cancer, testiclular cancer and lung cancer; wherein said polynucleotide is from 35 to 3000 nucleotides in length and comprises at least two CpG dinucleotides, and wherein said polynucleotide comprise a sequence which is identical to or complementary to a target sequence located within a sequence selected from the group consisting of SEQ. ID. NO.:1, SEQ. ID. NO.:2, SEQ. ID. NO.:3, SEQ. ID. NO.:4, SEQ. ID. NO.:5, SEQ. ID. NO.:6, SEQ. ID. NO.:7, SEQ. ID. NO.:8, SEQ. ID. NO.:9, SEQ. ID. NO.:10, SEQ. ID. NO:11, SEQ. ID. NO.: 12, SEQ. ID. NO.:13, SEQ. ID. NO.:14, SEQ. ID. NO.:15, SEQ. ID. NO.: 16, SEQ. ID. NO.:17, SEQ. ID. NO.:18, SEQ. ID. NO.: 19, SEQ. ID. NO.:20, SEQ. ID. NO.:21, SEQ. ID. NO.:22, SEQ. ID. NO.:23, SEQ. ID. NO.:24, SEQ. ID. NO.:25, SEQ. ID. NO.:26, SEQ. ID. NO.:27, SEQ. ID. NO.:28, SEQ. ID. NO.:29, SEQ. ID. NO.:30, SEQ. ID. NO.:31, SEQ. ID. NO.:32, SEQ. ID. NO.:33, SEQ. ID. NO.:34, SEQ. ID. NO.:35, SEQ. ID. NO.:36, SEQ. ID. NO.:37, SEQ. ID. NO.:38, SEQ. ID. NO.:39, SEQ. ID. NO.:40, SEQ. ID. NO.:41, SEQ. ID. NO.:42, SEQ. ID. NO.:43, SEQ. ID. NO.:44, SEQ. ID. NO.:45, SEQ. ID. NO.:46, SEQ. ID. NO.:47, SEQ. ID. NO.:48, SEQ. ID. NO.:49, SEQ. ID. NO.:50, SEQ. ID. NO.:51, SEQ. ID. NO.:52, SEQ. ID. NO.:53, SEQ. ID. NO.:54, SEQ. ID. NO.:55, SEQ. ID. NO.:56, SEQ. ID. NO.:57, SEQ. ID. NO.:58, SEQ. ID. NO.:59, SEQ. ID. NO.:60, SEQ. ID. NO.:61, SEQ. ID. NO.:62, , SEQ. ID. NO.:63, SEQ. ID. NO.:64, SEQ. ID. NO.:65, SEQ. ID. NO.:66, SEQ. ID. NO.:67, SEQ. ID. NO.:68, SEQ. ID. NO.:69, SEQ. ID. NO.:70, SEQ. ID. NO.:71, SEQ. ID. NO.:72, SEQ. ID. NO.:73, SEQ. ID. NO.:74, SEQ. ID. NO.:75, SEQ. ID. NO.:76, SEQ. ID. NO.:77, SEQ. ID. NO.:78, SEQ. ID. NO.:79, SEQ. ID. NO.:80, SEQ. ID. NO.:81, SEQ. ID. NO.:82, SEQ ID NO: 83, SEQ ID NO. 84, SEQ ID. NO. 85, SEQ. ID. NO. 86, SEQ. ID. NO. 87, SEQ. ID. NO. 88, SEQ. ID. NO. 89, SEQ. ID. NO. 90, SEQ. ID. NO. 91, SEQ ID. NO. 92, and SEQ. ID. NO. 93.

15. The isolated polynucleotide of claim 14 wherein said subject is suspected of having glioma and said polynucleotide comprises a sequence which is identical to or complementary to

a target sequence located within SEQ. ID.NO. 78, SEQ ID NO:71, SEQ ID NO:75, SEQ ID NO:18, SEQ ID NO:4, SEQ ID NO:22, SEQ ID NO:82, SEQ ID NO:27, SEQ ID NO:38, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:59, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:2, SEQ ID NO:7, SEQ ID NO:20, SEQ ID NO:30, SEQ ID NO:45, SEQ ID NO:72, SEQ ID NO:70, SEQ ID NO:26, SEQ ID NO:54, or SEQ ID NO:69.

16. The isolated polynucleotide of claim 14 wherein said subject is suspected of having acute myeloid leukemia and said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located within SEQ ID NO:10, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:58, SEQ ID NO:73, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:14, SEQ ID NO:24, SEQ ID NO:33, SEQ ID NO:56, SEQ ID NO:68, SEQ ID NO:76, SEQ ID NO:17, SEQ ID NO:52, SEQ ID NO:57, SEQ ID NO:26, SEQ ID NO:38, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:59, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:38, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:59, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:2, SEQ ID NO:7, SEQ ID NO:20, SEQ ID NO:30, SEQ ID NO:45, SEQ ID NO:72, SEQ ID NO:16, SEQ ID NO:55, SEQ ID NO:61, SEQ ID NO:63, or SEQ ID NO:70.

17. The isolated polynucleotide of claim 14 wherein said subject is suspected of having a primitive neuroectodermal tumor of childhood and said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located within SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:50, SEQ ID NO:9, SEQ ID NO:14, SEQ ID NO:24, SEQ ID NO:37, SEQ ID NO:4, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:72, SEQ ID NO:26, SEQ ID NO:15, SEQ ID NO:19, or SEQ ID NO:61.

18. The isolated polynucleotide of claim 14 wherein said subject is suspected of having breast cancer and said polynucleotide comprises a sequence identical or complementary to a target sequence which is located within SEQ ID NO:21, SEQ ID NO:28, SEQ ID NO:41, SEQ ID NO:80, SEQ ID NO:37, SEQ ID NO:63, SEQ ID NO:71, SEQ ID NO:75, SEQ ID NO:18, SEQ ID NO:4, SEQ ID NO:22, SEQ ID NO:82, SEQ ID NO:12, SEQ ID NO:23, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:43, SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:77.

19. The isolated polynucleotide of claim 14 wherein said subject is suspected of having colon cancer and said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located within SEQ ID NO:11, SEQ ID NO:40, SEQ ID NO:74, SEQ ID NO:81,

SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:76, SEQ ID NO:17, SEQ ID NO:52, SEQ ID NO:57, SEQ ID NO:37, SEQ ID NO:75, SEQ ID NO:18, SEQ ID NO:4, SEQ ID NO:27, SEQ ID NO:38, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:59, SEQ ID NO:36, or SEQ ID NO:46.

20. The isolated polynucleotide of claim 14 wherein said subject is suspected of head and neck cancer and said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located within in SEQ ID NO:1, SEQ ID NO. 79, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:76, SEQ ID NO:8, or SEQ ID NO:13.

21. The isolated polynucleotide of claim 14 wherein said subject is suspected of testiclular cancer and said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located within in SEQ ID NO. 29, SEQ ID NO:33, SEQ ID NO:56, SEQ ID NO:68, SEQ ID NO:51, SEQ ID NO:57, SEQ ID NO:70, SEQ ID NO:54, or SEQ ID NO:69

22. The isolated polynucleotide of claim 14 wherein said subject is suspected of having a lung cancer and said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located within SEQ ID NO: 83, SEQ ID NO. 84, SEQ ID. NO. 85, SEQ. ID. NO. 86, SEQ. ID. NO. 87, SEQ. ID. NO. 88, SEQ. ID. NO. 89, SEQ. ID. NO. 90, SEQ. ID. NO. 91, SEQ ID. NO. 92, and SEQ. ID. NO. 93.

23. An isolated CpG diagnostic oligonucleotide for characterizing cells which are obtained from a subject suspected of having a cancer selected from the group consisting of glioma, acute myeloid leukemia, primitive neuroectodermal tumors of childhood, breast cancer, colon cancer, head and neck cancer, testiclular cancer and lung cancer; wherein said olignoucleotide is from 15 to 34 nucleotides in length and comprises at least two CpG dinucleotides, and wherein said oligonucleotide comprise a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 of a sequence selected from the group consisting of SEQ. ID. NO.:1, SEQ. ID. NO.:2, SEQ. ID. NO.:3, SEQ. ID. NO.:4, SEQ. ID. NO.:5, SEQ. ID. NO.:6, SEQ. ID. NO.:7, SEQ. ID. NO.:8, SEQ. ID. NO.:9, SEQ. ID. NO.:10, SEQ. ID. NO:11, SEQ. ID. NO.: 12, SEQ. ID. NO.:13, SEQ. ID. NO.:14, SEQ. ID. NO.:15, SEQ. ID. NO.: 16, SEQ. ID. NO.:17, SEQ. ID. NO.:18, SEQ. ID. NO.: 19, SEQ. ID. NO.:20, SEQ. ID. NO.:21, SEQ. ID. NO.:22, SEQ. ID. NO.:23, SEQ. ID. NO.:24, SEQ. ID. NO.:25, SEQ. ID. NO.:26, SEQ. ID. NO.:27, SEQ. ID. NO.:28, SEQ. ID. NO.:29, SEQ. ID. NO.:30,

SEQ. ID. NO.:31, SEQ. ID. NO.:32, SEQ. ID. NO.:33, SEQ. ID. NO.:34, SEQ. ID. NO.:35, SEQ. ID. NO.:36, SEQ. ID. NO.:37, SEQ. ID. NO.:38, SEQ. ID. NO.:39, SEQ. ID. NO.:40, SEQ. ID. NO.:41, SEQ. ID. NO.:42, SEQ. ID. NO.:43, SEQ. ID. NO.:44, SEQ. ID. NO.:45, SEQ. ID. NO.:46, SEQ. ID. NO.:47, SEQ. ID. NO.:48, SEQ. ID. NO.:49, SEQ. ID. NO.:50, SEQ. ID. NO.:51, SEQ. ID. NO.:52, SEQ. ID. NO.:53, SEQ. ID. NO.:54, SEQ. ID. NO.:55, SEQ. ID. NO.:56, SEQ. ID. NO.:57, SEQ. ID. NO.:58, SEQ. ID. NO.:59, SEQ. ID. NO.:60, SEQ. ID. NO.:61, SEQ. ID. NO.:62, , SEQ. ID. NO.:63, SEQ. ID. NO.:64, SEQ. ID. NO.:65, SEQ. ID. NO.:66, SEQ. ID. NO.:67, SEQ. ID. NO.:68, SEQ. ID. NO.:69, SEQ. ID. NO.:70, SEQ. ID. NO.:71, SEQ. ID. NO.:72, SEQ. ID. NO.:73, SEQ. ID. NO.:74, SEQ. ID. NO.:75, SEQ. ID. NO.:76, SEQ. ID. NO.:77, SEQ. ID. NO.:78, SEQ. ID. NO.:79, SEQ. ID. NO.:80, SEQ. ID. NO.:81, SEQ. ID. NO.:82; SEQ ID NO: 83, SEQ ID NO. 84, SEQ ID. NO. 85, SEQ. ID. NO. 86, SEQ. ID. NO. 87, SEQ. ID. NO. 88, SEQ. ID. NO. 89, SEQ. ID. NO. 90, SEQ. ID. NO. 91, SEQ ID. NO. 92, and SEQ. ID. NO. 93; or a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

24. The isolated oligonucleotide of claim 23 wherein said subject is suspected of having glioma and said oligonucleotide comprises a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 in SEQ ID 78, SEQ ID NO:71, SEQ ID NO:75, SEQ ID NO:18, SEQ ID NO:4, SEQ ID NO:22, SEQ ID NO:82, SEQ ID NO:27, SEQ ID NO:38, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:59, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:2, SEQ ID NO:7, SEQ ID NO:20, SEQ ID NO:30, SEQ ID NO:45, SEQ ID NO:72, SEQ ID NO:70, SEQ ID NO:26, SEQ ID NO:54, or SEQ ID NO:69, or said oligonucleotide comprises a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

25. The isolated oligonucleotide of claim 23 wherein the subject is suspected of having acute myeloid leukemia; and said oligonucleotide comprises a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 SEQ ID NO:10, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:58, SEQ ID NO:73, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:14, SEQ ID NO:24, SEQ ID NO:33, SEQ ID NO:56, SEQ ID NO:68, SEQ ID NO:76, SEQ ID NO:17, SEQ ID NO:52, SEQ ID NO:57, SEQ ID NO:26,

SEQ ID NO:38, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:59, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:38, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:59, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:2, SEQ ID NO:7, SEQ ID NO:20, SEQ ID NO:30, SEQ ID NO:45, SEQ ID NO:72, SEQ ID NO:16, SEQ ID NO:55, SEQ ID NO:61, SEQ ID NO:63, or SEQ ID NO:70, or said oligonucleotide comprises a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

26. The isolated oligonucleotide of claim 23 wherein said subject is suspected of having primitive neuroectodermal tumors of childhood; and said oligonucleotide comprises a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 of SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:50, SEQ ID NO:9, SEQ ID NO:14, SEQ ID NO:24, SEQ ID NO:37, SEQ ID NO:4, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:72, SEQ ID NO:26, SEQ ID NO:15, SEQ ID NO:19, or SEQ ID NO:61, or said nucleotide comprises a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

27. The isolated oligonucleotide of claim 23 wherein said subject is suspected of having breast cancer; and said oligonucleotide comprises a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 of SEQ ID NO:21, SEQ ID NO:28, SEQ ID NO:41, SEQ ID NO:80, SEQ ID NO:37, SEQ ID NO:63, SEQ ID NO:71, SEQ ID NO:75, SEQ ID NO:18, SEQ ID NO:4, SEQ ID NO:22, SEQ ID NO:82, SEQ ID NO:12, SEQ ID NO:23, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:43, SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:77, or said oligonucleotide comprises a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

28. The isolated oligonucleotide of claim 23 wherein said subject is suspected of having colon cancer; and said oligonucleotide comprises a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 of SEQ ID NO:11, SEQ ID NO:40, SEQ ID NO:74, SEQ ID NO:81, SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:76, SEQ ID NO:17, SEQ ID NO:52, SEQ ID NO:57, SEQ ID NO:37, SEQ ID NO:75, SEQ ID NO:18, SEQ ID NO:4, SEQ ID NO:27, SEQ ID NO:38, SEQ ID NO:47, SEQ ID

NO:49, SEQ ID NO:59, SEQ ID NO:36, SEQ ID NO:46 or said oligonucleotide comprises a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

29. The isolated oligonucleotide of claim 23 wherein said subject is suspected of having head and neck cancer; and said oligonucleotide comprises a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 in SEQ ID NO:1, SEQ ID NO. 79, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:76, SEQ ID NO:8, or SEQ ID NO:13., or said nucleotide a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

30. The isolated oligonucleotide of claim 23 wherein said subject is suspected of having testiclular cancer; and said oligonucleotide comprises a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 in SEQ ID NO. 29, SEQ ID NO:33, SEQ ID NO:56, SEQ ID NO:68, SEQ ID NO:51, SEQ ID NO:57, SEQ ID NO:70, SEQ ID NO:54, or SEQ ID NO:69, or said oligonucleotide comprises a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

31. The isolated oligonucleotide of claim 23 wherein said subject is suspected of having lung cancer; and said oligonucleotide comprises a sequence which is identical to a target sequence located within a region extending from nucleotide 1 through nucleotide 99 of SEQ ID NO SEQ ID NO: 83, SEQ ID NO. 84, SEQ ID. NO. 85, SEQ. ID. NO. 86, SEQ. ID. NO. 87, SEQ. ID. NO. 88, SEQ. ID. NO. 89, SEQ. ID. NO. 90, SEQ. ID. NO. 91, SEQ ID. NO. 92, and SEQ. ID. NO. 93, or said oligonucleotide comprises a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

32. A method for determining whether cells obtained from a subject suspected of having a cancer are malignant or non-malignant, comprising:

a) digesting DNA which has been isolated from the cells with a methylation-sensitive restriction enzyme to provide a set of restriction fragments;

b) hybridizing said restriction fragments with a CpG diagnostic polynucleotide comprising a sequence which is identical to or complementary to a target sequence on one of the

strands of a diagnostic control fragment identified according to the method of claim 2, wherein said method employed said methylation-sensitive restriction enzyme, wherein said target sequence comprises at least two CpG dinucleotides, wherein said polynucleotide is from 35 to 3000 nucleotides in length, and wherein said reaction is conducted under stringent hybridization conditions; and

c) assaying the reaction products of step b to determine the size or the sequence of the restriction fragment to which the CpG diagnostic polynucleotide has hybridized.

33. The method of claim 32 wherein said subject is suspected of having a cancer selected from the group consisting of glioma, acute myeloid leukemia, primitive neuroectodermal tumors of childhood, breast cancer, colon cancer, head and neck cancer, and testiclular cancer;

wherein said DNA sample is digested with NotI; and

wherein said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located in SEQ. ID. NO.:1, SEQ. ID. NO.:2, SEQ. ID. NO.:3, SEQ. ID. NO.:4, SEQ. ID. NO.:5, SEQ. ID. NO.:6, SEQ. ID. NO.:7, SEQ. ID. NO.:8, SEQ. ID. NO.:9, SEQ. ID. NO.:10, SEQ. ID. NO:11, SEQ. ID. NO.: 12, SEQ. ID. NO.:13, SEQ. ID. NO.:14, SEQ. ID. NO.:15, SEQ. ID. NO.: 16, SEQ. ID. NO.:17, SEQ. ID. NO.:18, SEQ. ID. NO.: 19, SEQ. ID. NO.:20, SEQ. ID. NO.:21, SEQ. ID. NO.:22, SEQ. ID. NO.:23, SEQ. ID. NO.:24, SEQ. ID. NO.:25, SEQ. ID. NO.:26, SEQ. ID. NO.:27, SEQ. ID. NO.:28, SEQ. ID. NO.:29, SEQ. ID. NO.:30, SEQ. ID. NO.:31, SEQ. ID. NO.:32, SEQ. ID. NO.:33, SEQ. ID. NO.:34, SEQ. ID. NO.:35, SEQ. ID. NO.:36, SEQ. ID. NO.:37, SEQ. ID. NO.:38, SEQ. ID. NO.:39, SEQ. ID. NO.:40, SEQ. ID. NO.:41, SEQ. ID. NO.:42, SEQ. ID. NO.:43, SEQ. ID. NO.:44, SEQ. ID. NO.:45, SEQ. ID. NO.:46, SEQ. ID. NO.:47, SEQ. ID. NO.:48, SEQ. ID. NO.:49, SEQ. ID. NO.:50, SEQ. ID. NO.:51, SEQ. ID. NO.:52, SEQ. ID. NO.:53, SEQ. ID. NO.:54, SEQ. ID. NO.:55, SEQ. ID. NO.:56, SEQ. ID. NO.:57, SEQ. ID. NO.:58, SEQ. ID. NO.:59, SEQ. ID. NO.:60, SEQ. ID. NO.:61, SEQ. ID. NO.:62, , SEQ. ID. NO.:63, SEQ. ID. NO.:64, SEQ. ID. NO.:65, SEQ. ID. NO.:66, SEQ. ID. NO.:67, SEQ. ID. NO.:68, SEQ. ID. NO.:69, SEQ. ID. NO.:70, SEQ. ID. NO.:71, SEQ. ID. NO.:72, SEQ. ID. NO.:73, SEQ. ID. NO.:74, SEQ. ID. NO.:75, SEQ. ID. NO.:76, SEQ. ID. NO.:77, SEQ. ID. NO.:78, SEQ. ID. NO.:79, SEQ. ID. NO.:80, SEQ. ID. NO.:81, and SEQ. ID. NO.:82.

34. The method of claim 32 wherein the subject is suspected of having lung cancer;

wherein the DNA is digested with AscI;

and wherein said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located in , SEQ ID NO: 83, SEQ ID NO. 84, SEQ ID. NO. 85, SEQ. ID. NO. 86, SEQ. ID. NO. 87, SEQ. ID. NO. 88, SEQ. ID. NO. 89, SEQ. ID. NO. 90, SEQ. ID. NO. 91, SEQ ID. NO. 92, and SEQ. ID. NO. 93.

35. A method of determining whether cells contained within a tissue sample obtained from a subject suspected of having cancer are malignant, comprising:

a) treating DNA isolated from the tissue sample with a compound which converts non-methylated cytosines to a different nucleotide base;

b) reacting a portion of the treated DNA with a CpG diagnostic oligonucleotide which is complementary to a target sequence which comprises CpG islands that are preferentially methylated in malignant cells of subjects known to have said cancer;

c) reacting a portion of the treated DNA with a modified CpG diagnostic oligonucleotide which is complementary to a modified target sequence in which the cytosines in said target sequence are replaced with the different nucleotide base; and

d) assaying the reaction products of step b and step c to determine whether the treated DNA has hybridized with the CpG diagnostic oligonucleotide or the modified CpG diagnostic oligonucleotide; wherein hybridization of the treated DNA with the CpG diagnostic oligonucleotide as opposed to the modified CpG diagnostic oligonucleotide indicates that the DNA has been obtained from malignant cells.

36. The method of claim 35 wherein the chemical compound is sodium bisulfite and the non-methylated cytosines are converted to uracil.

37. The method of claim 35 wherein the assay is a polymerase chain reaction,

wherein a portion of the treated DNA is reacted with a first primer set which comprises two diagnostic CpG olignonucleotides; and

wherein a portion of the treated DNA is reacted with a second primer set which comprises two modified diagnostic CpG oligonucleotides.

38. The method of claim 35 wherein the subject is suspected of having a cancer selected from the group consisting of glioma, acute myeloid leukemia, primitive neuroectodermal tumors of childhood, breast cancer, colon cancer, head and neck cancer, testiclular cancer and lung cancer; and

wherein the CpG diagnostic oligonucleotide comprises a sequence which is identical to a target

sequence located between nucleotide 1 and 100 in a sequece selected from the group consisting said polynucleotide comprises a sequence which is identical to or complementary to a target sequence located in SEQ. ID. NO.:1, SEQ. ID. NO.:2, SEQ. ID. NO.:3, SEQ. ID. NO.:4, SEQ. ID. NO.:5, SEQ. ID. NO.:6, SEQ. ID. NO.:7, SEQ. ID. NO.:8, SEQ. ID. NO.:9, SEQ. ID. NO.:10, SEQ. ID. NO:11, SEQ. ID. NO.: 12, SEQ. ID. NO.:13, SEQ. ID. NO.:14, SEQ. ID. NO.:15, SEQ. ID. NO.: 16, SEQ. ID. NO.:17, SEQ. ID. NO.:18, SEQ. ID. NO.: 19, SEQ. ID. NO.:20, SEQ. ID. NO.:21, SEQ. ID. NO.:22, SEQ. ID. NO.:23, SEQ. ID. NO.:24, SEQ. ID. NO.:25, SEQ. ID. NO.:26, SEQ. ID. NO.:27, SEQ. ID. NO.:28, SEQ. ID. NO.:29, SEQ. ID. NO.:30, SEQ. ID. NO.:31, SEQ. ID. NO.:32, SEQ. ID. NO.:33, SEQ. ID. NO.:34, SEQ. ID. NO.:35, SEQ. ID. NO.:36, SEQ. ID. NO.:37, SEQ. ID. NO.:38, SEQ. ID. NO.:39, SEQ. ID. NO.:40, SEQ. ID. NO.:41, SEQ. ID. NO.:42, SEQ. ID. NO.:43, SEQ. ID. NO.:44, SEQ. ID. NO.:45, SEQ. ID. NO.:46, SEQ. ID. NO.:47, SEQ. ID. NO.:48, SEQ. ID. NO.:49, SEQ. ID. NO.:50, SEQ. ID. NO.:51, SEQ. ID. NO.:52, SEQ. ID. NO.:53, SEQ. ID. NO.:54, SEQ. ID. NO.:55, SEQ. ID. NO.:56, SEQ. ID. NO.:57, SEQ. ID. NO.:58, SEQ. ID. NO.:59, SEQ. ID. NO.:60, SEQ. ID. NO.:61, SEQ. ID. NO.:62, , SEQ. ID. NO.:63, SEQ. ID. NO.:64, SEQ. ID. NO.:65, SEQ. ID. NO.:66, SEQ. ID. NO.:67, SEQ. ID. NO.:68, SEQ. ID. NO.:69, SEQ. ID. NO.:70, SEQ. ID. NO.:71, SEQ. ID. NO.:72, SEQ. ID. NO.:73, SEQ. ID. NO.:74, SEQ. ID. NO.:75, SEQ. ID. NO.:76, SEQ. ID. NO.:77, SEQ. ID. NO.:78, SEQ. ID. NO.:79, SEQ. ID. NO.:80, SEQ. ID. NO.:81, SEQ. ID. NO.:82, SEQ ID NO: 83, SEQ ID NO. 84, SEQ ID. NO. 85, SEQ. ID. NO. 86, SEQ. ID. NO. 87, SEQ. ID. NO. 88, SEQ. ID. NO. 89, SEQ. ID. NO. 90, SEQ. ID. NO. 91, SEQ ID. NO. 92, and SEQ. ID. NO. 93; or a sequence which is the reverse complement of a target sequence located in a region extending from about nucleotide 100 through nucleotide 500 in said SEQ ID NO.

39. An isolated polynucleotide for characterizing cells which are obtained from a subject suspected of having a cancer selected from the group consisting of glioma, acute myeloid leukemia, primitive neuroectodermal tumors of childhood, breast cancer, colon cancer, head and neck cancer, testiclular cancer and lung cancer; wherein said polynucleotide is from 35 to 1000 nucleotides in length and comprises at least two CpG dinucleotides, and wherein said polynucleotide comprise a sequence which is identical to or complementary to a target sequence which originates between nucleotide 1 and nucleotide 15 of SEQ. ID. NO.:1, SEQ. ID. NO.:2, SEQ. ID. NO.:3, SEQ. ID. NO.:5, SEQ. ID. NO.:6, SEQ. ID. NO.:7, SEQ. ID. NO.:8, SEQ. ID.

NO.:9, SEQ. ID. NO.:10, SEQ. ID. NO:11, SEQ. ID. NO.: 12, SEQ. ID. NO.:13, SEQ. ID. NO.:14, SEQ. ID. NO.:17, SEQ. ID. NO.:18, SEQ. ID. NO.: 19, SEQ. ID. NO.:20, SEQ. ID. NO.:21, SEQ. ID. NO.:22, SEQ. ID. NO.:23, SEQ. ID. NO.:24, SEQ. ID. NO.:25, SEQ. ID. NO.:27, SEQ. ID. NO.:28, SEQ. ID. NO.:29, SEQ. ID. NO.:30, SEQ. ID. NO.:31, SEQ. ID. NO.:32, SEQ. ID. NO.:33, SEQ. ID. NO.:34, SEQ. ID. NO.:35, SEQ. ID. NO.:36, SEQ. ID. NO.:37, SEQ. ID. NO.:38, SEQ. ID. NO.:40, SEQ. ID. NO.:41, SEQ. ID. NO.:42, SEQ. ID. NO.:43, SEQ. ID. NO.:44, SEQ. ID. NO.:45, SEQ. ID. NO.:47, SEQ. ID. NO.:48, SEQ. ID. NO.:49, SEQ. ID. NO.:50, SEQ. ID. NO.:51, SEQ. ID. NO.:52, SEQ. ID. NO.:53, SEQ. ID. NO.:54, SEQ. ID. NO.:55, SEQ. ID. NO.:56, SEQ. ID. NO.:58, SEQ. ID. NO.:60, SEQ. ID. NO.:62, , SEQ. ID. NO.:63, SEQ. ID. NO.:64, SEQ. ID. NO.:65, SEQ. ID. NO.:66, SEQ. ID. NO.:67, SEQ. ID. NO.:69, SEQ. ID. NO.:70, SEQ. ID. NO.:72, SEQ. ID. NO.:73, , SEQ. ID. NO.:75, SEQ. ID. NO.:76, SEQ. ID. NO.:77, SEQ. ID. NO.:78, SEQ. ID. NO.:79, SEQ. ID. NO.:80, SEQ. ID. NO.:81, SEQ. ID. NO.:82, SEQ ID NO: 83, SEQ. ID. NO. 86, SEQ. ID. NO. 87, SEQ. ID. NO. 88, SEQ. ID. NO. 89, SEQ. ID. NO. 90, SEQ. ID. NO. 91, SEQ ID. NO. 92, and SEQ. ID. NO. 93.

SEQUENCE LISTING

<110> Ohio State Research Foundtaion
Plass, Christoph

<120> Detection of Methylated CpG Rich Sequences Diagnostic for Malignant Cells

<130> 22727/04075

<160> 90

<170> PatentIn version 3.0

<210> 1
<211> 677
<212> DNA
<213> Homo sapiens 2.B.53

<220>
<221> n
<222> (1)..(677)
<223> a or g or c or t

<400> 1
gcggccgcgg ttagcttctc ctgtccgaac gcagggtttc actggggcgc cgctacggtt 60

cctatggcaa cgcggctcct cgacgcagcc caggagtcgc ggtcgcggga ggctgcgccg 120

cgcaccgagc tcttccctgt ggccgccgca gccgccagcc tcttcctgct catgcttttc 180

ctcatcttca tctcggtctg agtgggctct ggacctctcc accagcctct gccccagaac 240

tgttaactgc gggggggaaa aaaggaattt gtcgtcgcaa cgcgcgttcc gatggagccg 300

cacgccacaa aggaagactc atgctgcacc ccgcggggca gatgcggcga cactggacat 360

cgctgcacag ctgggtctgc ccgtttccag agctgcttag cgccgacgcc cataaatgag 420

gaggactccc tgtgtattaa aaggggggatc cgcagggttt aatttgataa ggattatagc 480

cttcataaag gcatttttaa caaaaagatg taggtggcat ggtaatcgag tattatttac 540

gcatctctcc gcacacgcac tcatacctga aaacgttntg gcaggcacaa aatgattttt 600

ttgtgtataa aagaatgtgt gtaactcgtg gatggtgggg ttcagcagga caagatagtg 660

acattagata aattaca 677

<210> 2
<211> 380
<212> DNA
<213> Homo sapiens 2.C.24

<220>
<221> n
<222> (1)..(380)
<223> a or g or c or t

<400> 2
gcggccgcct tgaaggcgct ggacgggatg gtgctgaagt cggtgaagga gccccggcag 60

gtgagctcgc ggcccgccag cccgctgccc acgcagtagt ggaagaggcc gaagtagcca 120

ggcttggggg tgctcacgct gtcgcccacc cagtagggct ggatgaagac caccacgttg 180

atgatggcga agcagatggt gaagatggcc cacagcacgc cgatggcccg cgagttccgc 240

atgtantgct cgtggtagag cttggaacct cctgcgaggg cagcatggtg cccggangcg 300

gggccggcgg cggctgtngc tggcngnggc cgtcggcccg ggacngacgc ctggctgccg 360

ggcgggaact ggggactcac 380

<210> 3
<211> 566
<212> DNA
<213> Homo sapiens 2.C.29

<400> 3
gcggccgccg cgctagtgac tacttcctcc tactccttct cctcctgctc cggcctcctg 60

gcgccctgct ccaggctctc cggcgccctg ctccaggctc tccggcgccc tccagccagg 120

caccggccga accgggtagt gccgcaaggt gtaattactg ctttgaaact ttaaaggcat 180

ttggaaagaa actacgggtt atgcttactt tttttgtttt tgattattat tttgtaggag 240

acacaaagtt taaaaataga aagcaaaaag tgtgacacat ttaaagagtt aaaggaaata 300

aacgtttcca atttacctta taacatgatt ttcatacact ggatttgttt aaaacagact 360

gactacatgg ataacttttc taggaattgt tcttaactct gatagctggc tcaactgatg 420

taggcattaa aataacgtca tattaccatc tttcctccac gaattgatga tatttgacta 480

tagctttgtc agggttatgt ccaactattg tataatatgt gtcagtttcc tattgctacc 540

gtaacaaatt accccaaatt tactgg 566

<210> 4
<211> 1297
<212> DNA
<213> Homo sapiens 2.C.35

<220>
<221> n
<222> (1)..(1297)
<223> a or g or c or t

<400> 4
gttcacttct cgctgcgccg cgggttctgt agaagcgcaa gaatggggct gattattccg 60

gtgcccacat gccgcccccа cacgccccca cccccgtccg gcgcaagact tcccttggcc 120

aaaagaggcg tttaattagt tctggggccg cggagagcca gcgtggccga caaagcccgg 180

ctccccaggt aacccgggtt ccctgcggac ccgggagggg gcgcgcgggg ccggagcacc 240

ggccttgggc tgcgcgctcc ctccggcgac actgccgtcc ccctggcctc cggcccggtc 300

ccccgcaggc caaaggctca tctgccgggc ttgggtggcc cgggccagcg ccgcctgcgg 360

tccccgagtg cggctggctc taaggccggc gccctctccc cggctttcag tgctcagagc 420

caggccagcg ggaaagaagg cagcatggtc cgcaaaagac aggtggcagt ggcagtcttg 480

catgatactt gtccttcttc cctgttcccc attttgggga aacactggaa acacttttct 540

ctttatgcgc attcgcgtct cagcaccgag tgctccaagc cctgcgcgca gcgccgggct 600

tggaaggcgg cgaatggctg cctagccgcc gcccctacta gtgacactcg gccgccagcc 660

cccgcccagg atgtgcacat ctgctggcag cactggcccg ggtggcagtc accgggccac 720

ccactccaca ggtacaaccg cacccaatcc aacctggaac tcggagggct gtgcgcgccg 780

agctgggatc gcgccccaac gagccgggcc tttggctgcg ccagggccca ggccgagtca 840

tccccccgct cgcgtcgccg cgaggcggga caccgtgtaa tacctttgcc gtgggctggg 900

cgtcggccgc gggccggaga gcgggtgtcc cacctcgcct catcatttga tttccgccag 960

cgtctgagga cggcgcaccc aattcgttcc actcgctgcg ctctgtgaac cagcggcggg 1020

cagggcgggg gaggccgggc tggggnaggg cagggtggtc ccaatccccc gcccccgccc 1080

cgccggcctc gcggagcaca agtgttggga ttcccacggg caggcgtgct ctgcggctgg 1140

aggcccgagc gcccagggcc caggagacgt ggcggacaca gaggggtttg taggcacggt 1200

gacctccgtg ctcctgctct gaaagggcct gaaaggagcg gtttatggtg cattaccagt 1260

caagggctca ggtaccagcg cctgtgtcgg gaacccg 1297

<210> 5
<211> 651
<212> DNA
<213> Homo sapiens 2.C.54

<400> 5
gcggccgccg cgggggacgc tcagatctcg cgagaagagg gcgagcgcgc tgccccctg 60

gtgggcgggg cgaagcccgg gagagggtgg gcgccaccgg aggggaggag gggaacaggg 120

aactgaagga agtgggaggg gccggcgggg cggggaagcg gaaaggggc gtggctgagg 180

gcgggaggat taagctgcct ttttgaaagt ggagcgccag gtcccgggtt ctgggtggag 240

gtggttgctg attggtggag ctcggagcgg cggttgggag ggtcctggtc acatggtggg 300

gagtgggagg ggggaagttc ggagagcggg agcgggatgg tagtgggctg ggccccactg 360

ggctgggaca gcaggaggat agtcttgagg aggagcgtgg ggtgctagat gtgtaactac 420

gtcccgaact ggttcctgtg tttttctagg gcatgtggac tagggatggg tacttgagta 480

gaagcctgca acttgaagag tttgtgcagg agttagctgc agtgtcggaa attagtgtcc 540

tgtatgctca acaaggtatt cggactgggt gtgcacacca cagctctcag gactggaagg 600

tggaaattta atctacgaag ttcccttaaa ctgcataagc ttcgggacct c 651

<210> 6
<211> 710
<212> DNA
<213> Homo sapiens 2.C.57

<220>
<221> n
<222> (1)..(710)
<223> a or g or c or t

<400> 6
gcggccgcac ggagttgaag acactaaccc agctaagcca catacagacc ctcacggccg 60

cctggtctac acaggccgcc acagctacac aggctcaggc ctcagcctgg tcacaatggt 120

cacacccaca ctctcgggtc ccacagtttt gcgggagcgg tgacacacac ccgctcccaa 180

ctgaccacgc ccacacacgc tggcttcagc cgcacacgca cacagtagcc acgccccctt 240

atgctccagc cttgccagca cccgccctcg ccacgctggt cacgcccaca cacacacaca 300

cacacacaca cacacgcacg caggcctggg gcacgcccct cccccacacg caggcgtgcg 360

gcacgccttc ccatacacac acacacgcgc gcgggcctgg ggcacgccct ccacacacat 420

gcaggggtag ggcacgcccc cacacacaca cacgccggcc tggggcacgc tcgcgcgcac 480

atgcacacac atacacacgc acaggcctgg ggcaggcccc acccccacac acgcaggcct 540

ggggcacgcc cccccacaca tgcaggcctg gagcatgcgc acactcgcag gccttgggca 600

cacgcgcaca cactcatgca cagacacgca cgcacacatc gagccccgcc cncggaagca 660

catgagaggc acttgctttc actgactgan ggcanggctt tgggcccgcn 710

<210> 7
<211> 1204
<212> DNA
<213> Homo sapiens 2.C.58

<400> 7
gcggccgctc ctctttattc tactctcacc cgaggcccgc gcccgtcccg gggagcggct 60

ctgccaggaa aacggcccga ccagtgcccg gcgcctgggc tgcgtccgag cccaccttct 120

tccctcgtcg tcgtctccca gactaaatcc cggaaaggga aagcgggatg tttgcgccca 180

ccgcgctgta gctggtcctg acacttgcaa aatggtcagt ggctcctgct cggccaggct 240

gagtgtgtgc gtgtgtgtga gcaagggagc gagggtgtgc ggtgtgcagg gggtgcgctg 300

tgtgtgcgcg cgtctccggg aaggtctcgc ggcggctgga gccgggactg acagcccggg 360

cggagcgcag gcagctccac acgctaaacc tctcgcctct cccctcaccc ccaccccttc 420

cactcccctc tccttccccc accctccccg gccccttcca agctctctga ttggccaatg 480

ggacaaaagt ttctgtggag acggctgggc gctgacgtca cgggcagaat tgtcccattt 540

agggatcccs ggggcagtgc gcatgctgca ggctgcaggt tagaggcaga aggaggtagc 600

agcgggcccg gcggcagcca ggtggcagaa aggagcacgc agcatccagg tgggggggacg 660

actccagcag ggtttccatg gagattcctc tgggtctagc ctaaaaacag cagatcagct 720

gacaccatta gctcaggacc taattactgc ttattggagc aacaaatgag ggaaagggcc 780

agctgcaaag gaagagtttt tatcccccca ccccattccc ccatctcctt tctccccctc 840

tctccatccc tcttgagtcc cgggtgaatt ctcattaact tgcaagattc ctgcaacaac 900

agctcccctt ctccagaggc caccccgact gcttttattc ttttatttcc ttcttttgta 960

ttaaaaagaa atgctaaaat aaatcagttg ttgagtcctt gaatttttgt tcaatacgta 1020

ttagaccata gagctcagag aagacactgt ccaatgaagt cacaagtgaa tctaatacaa 1080

gggactcagg ggaaaaatat cactttcaat ttattgaggt gaatctttag atatttcaca 1140

ttaaaaaaat cttaatatct taaatacata aatatttgaa acacgcaatt ggacagaaga 1200

tatc 1204

<210> 8
<211> 687
<212> DNA
<213> Homo sapiens 2.C.59

<220>
<221> n
<222> (1)..(687)
<223> a or g or c or t

<400> 8
gcggccgcac aagcgcacac gcacacgtcc agggcggagg aacactacta gtaacacccg 60

cctccttcta gcctccctat cccaaagtta tggtgccgat tttgtccgcg gcaggggctc 120

caggggcaca ctcataaatt cggtgcggag gaacacaact agcagcacca caccccgcc 180

actgccagaa ccaaagtgac ggtgccgaca cccctccgca agcgcaaggc cgacttccat 240

aagtaattag ccagagcacc gtcccgttcc tgtcagcacc gagccccagc caggacaccg 300

gtattcccag caccatacaa gaactacttt ttcgatgaag caacccaaaa gctgcgagcg 360

gttcccggtg aggccgccca ctcacctggc cggcgcagac aagctccgtg cgtcaagaca 420

taacagcgta agtgtacgac gttgcgcagc gacgcggggg ccttcgggaa atgtagtcta 480

caactggaaa ccggccggat cgtgtctgcg caggcccagc agctaagatc gggtccggcg 540

ctccagaaca gaacgatccc tgaggctccc ttgctcgaac tgtgggactt accctactat 600

ggtccgagcc taccctattt cattatactc aagtaacgcc ccagaaattn cagagaatct 660

acacaaagag gttgagtctt gccgtgg 687

<210> 9
<211> 1520
<212> DNA
<213> Homo sapiens 2.D.10

<400> 9
gcggccgcga ggacagctcg gacgggggag agaaaggagg tttccagtaa aaataataac 60

gccagagaga aaaccgtaac tcgcgtgaca cagacagaaa tttccagtaa taatcatcag 120

gtgatagaga aggaaggctt ccaaaatgaa gaacaagtga aataaaggtt ttagtcatga 180

attacagcac gtgcgatgga tgagtggtga tttctcatca taaatggtaa ctcgggagat 240

agagaaacgt gtccagccct aaactacaac agggtttggt ttgaaagaga ggtgctgtca 300

taaagcggaa ctcaggggat ggggaagacg gcctccgtcc caaatgacaa ctcaatgaca 360

gagaacaaaa gatccaaact aaagtgatgg agaaaaaggg tttccaacca ccacacaaat 420

gaagagaaag actgatcaca taatgaagta ttcagtcatt aatacatgat aaacccggtg 480

atagagaaag aggcttagtc acaaattact cagataatgg agaaaaaagc cttattcatg 540

tatcactcag gtagatacat caaggcaggt ttcctgccat aaaggataac acagctaaaa 600

gagaaataaa ggttttagta ataagtgaca attcatataa cagagaaaga aggcttctgg 660

ccataaggat aactcatgta ataaagaaaa gttttagtca taaataatag agaaagaaag 720

gtttccgata gaaaatggta gagatagaaa ggttctaggt aacaaacggt aactgaagtg 780

atagagcaag gtcacaaata ataactcagg taatagagaa agatttctag tcataaataa 840

tacatctgct acagaaataa gggttttgat tcataaagtt atgtcataag tgataagtgg 900

tagaaaagga aaggttttag ttataaatta tgattcaagg gatagaaaaa caaaggtttc 960

aagttataaa tatcatttca atggtcaaga aaggttttca gtcatgaatg aaaactgggt 1020

gaagttttcc agtcacaggt tataactcag gcaatggaca gagaaggaaa gatttttgtc 1080

atcaatcaac tcaggtggag aaggaaaggt ttttcaataa gaaataactc agttgagtga 1140

aagaaggctt gaggtcatga atgataatta ggtgatagag aaagaaatgt tccagtcata 1200

agggttaaat cagatgctag agaaagaaag gtttttagtc ataaataaaa ctcagctgct 1260

agaaagaata gggctaccag tcataattga taactcaggt gagagaaaga ttgctggtca 1320

taaattgtaa cccaggtgac agaaaagaag gtgtcactca cacatgataa ttcgggttat 1380

gaggaaggtt tccagccaca gtggtaactc aggtgctagg gaaagaaggt ttgggcaata 1440

atgacaactc aggtaataca gaaaaacgat tacagtcata aatgacagag aaggaaaggc 1500

ttttattcat aaaggatatc 1520

<210> 10
<211> 575
<212> DNA
<213> Homo sapiens 2.D.14

<400> 10
gcggccgcgg ctgtggctcc tcttggccgc gcagctgaca ggtaaggcgg cggcgcgcgg 60

gctacccaag ggtctgcgct cccggggcct gagcggggag gtgataagtg gctgtcctgg 120

ccctggtcct ggcagggtgc agcgtcgagc ccgcggtggc ggggcgcccg ggaggcagct 180

tggcaggcac ggtccctaag ggtggaaata aaataccccc atatcgcatt accccggggg 240

accggagagc ccctggactg aggccacctc ccctcaaaag cctggacgca ggagaagggg 300

aggcagtgaa aaggggagcg agtgagggaa ggaaagagag ggtcgctgga ggtcaccagg 360

ggaaggaaac aggtccctgc ccagggtccc cgcaggatgt gctcggagga aggttggcca 420

ggccatgggt cctgtggaca catttttatt acttccgggg aagtgtttgt agtacaatca 480

gacaaacatc gggcgttctc agttctcgga gggctagggc agggtgatcc ctctggctcc 540

cgttctccct gatgtcgctg gtgttgggtg tcatg 575

<210> 11
<211> 741
<212> DNA
<213> Homo sapiens 2.D.20

<220>
<221> n
<222> (1)..(741)
<223> a or g or c or t

<400> 11
gcggccgcgt cgtcgctgag tacaccagct gcctcatcta tctggagccc ggcctccatc 60

tcgccaggct cagcgcccgc gtccgtgtcg gtgccggagc cattggccgc gcctagcaac 120

acctcgtgta tgcagcgctc cgtagctgca ggcgccgcca ccgcagcagc ctcttatccc 180

atgtcctacg gccagggcgg cagctacggc caaggctacc ctacgccctc ctcttcctac 240

tttggcggcg tggactgcag ctcataccta gcgcccatgc actcacatca ccacccgcac 300

cagctgagcc ccatggcacc ctcctccatg gcgggccacc atcatcacca cccacatgcg 360

caccacccgt tgagccagtc ctcaggccac caccaccacc atcaccacca ccaccaccaa 420

ggctacggtg gctctgggct tgccttcaac tctgccgact gcttggatta caaggagcct 480

ggcgccgctg ctgcttcctc cgcctggaaa ctcaacttca actcccccga ctgtctggac 540

tataaggacc aagcctcatg gcggttccag gtcttgtgag cccaggaatg aaagaggaga 600

agaaacgcaa ctacctgcgc cctccgtggt cccgatcctg ttgctgctgc tgcaccgccc 660

gcctttgcct cgtcttctcc aaaaactgat tntcaccccc caaaagatgt ccattgcctg 720

cactgccgcc cncatttttg t 741

<210> 12
<211> 458
<212> DNA
<213> Homo sapiens 2.D.25

<220>
<221> n
<222> (1)..(458)
<223> a or g or c or t

<400> 12
gcggccgcca gtagcagagc ccagcacatt gcgggtgccc agttcatctt cgtggggtta 60

aacctgcggg aagagaggga aagggccctt agtttccatg gagatcgggt gcccaggggc 120

ggagggctca aggctggaga gcagagggac ccccatcttt tgtgggatca gggtgccccc 180

agcatcttgg aggcccactg aggcctgggg gggcgcggtt taacttctag catcagggac 240

ttaggcctgg gggaggcgct gggaagtggc aggtggggca ggagggttct gcacctgaag 300

gttgtgcacc tggattgggg gtgtagaagc ggngcaggag cgccgcggtg ggggcgtcca 360

ggcccgggcg gnggagcaag cctgggggag ggagctctgc acgcgttgct gggatgtggg 420

gggcgngggg aggcggcatg gggggagggg cgttgtgt 458

<210> 13
<211> 615
<212> DNA
<213> Homo sapiens 2.D.27

<400> 13
gcggccgccc ggcgtcccgc tctgggggggc cgggaccgaa gcgctcacgg cccggggacg 60

cggggttggt ccaggctgcg gcctgtggcg cgtgcaggcc tgaaggaggc gagatgccga 120

tgccgccacc gctggtccgg tggaccaggc cccttggtcc agcctcccct cccgcagccg 180

cccgtctggg ggtgttcgca gccccgggct cccccggccc gcccgccggg gagtgggagg 240

gcgatggcgc cccgcctccg gctcttacgg agagcgcgcc tccccctcaa ctccggcggc 300

ggtgagccgg ggtgcgatgc gcggccgagg cctcgcccgg accgccggtc cccatcgcgt 360

ccctgggcga gggaggggcg gttggccgga gatggcggag gggcgtaccc gccccgcctg 420

cccgccgtcc ccagccctca gcgcctgggg aagcccctgc tgtggcagtg ctcgggcgct 480

atccggagga agaggagcag ttcctctttc ttggctgcgg cagggctgct tgggccggaa 540

aactaacttg tgtcggcgcc cagccgcccc gcgccggctg ccggctagct caggccgacg 600

ccgaggggag cggcg 615

<210> 14
<211> 669
<212> DNA
<213> Homo sapiens 2.D.34

<400> 14
gcggccgcgc ggggcagcgc gaggaactgt tgatttgcct gcgccttggg cccctgcgtc 60

tctcccaggc ggcggctccc gctttcctca aaggccgtgt cgggtttgtt gtttggtgtg 120

ggtgccggga aagggcgctt ctccccagtg aggtggggaa cttgggtgat gggaccacgg 180

aggcgccggt tcgtgcccgg tggggacggg tgaggcaggg gagagtgaga ttttattctc 240

ccccaaggaa ggagtgtccc cttctcctta ttttgagggc tattcaagct tattgaaacc 300

agaaagcggt gtttcttgtc aatctctcag ccccttcttc caaccaagaa caattgtcga 360

tgagtttcca tcacaggcgc ttgtgagaga accggtaaac ccagtacagc aaaatccaag 420

cccttggttt ccacatgcat tttgctagca gtttttggca ttgaccctcg ccctcccgtg 480

tttccactcg acatcattta gcgtttgagg ttttttttccc tcctcaaaat tgcaaatgag 540

aaaaaaagag gaaaccagga aaaggggggtg gggggtagca tttaaattgg atgtgagttt 600

ctgctgagaa ttctagcgaa gtcccctgta cactgaagcg ccgagagatt tttccgtttg 660

tgtatcttc 669

<210> 15
<211> 998
<212> DNA
<213> Homo sapiens 2.D.40

<220>
<221> n
<222> (1)..(998)
<223> a or g or c or t

<400> 15
gatatccatt ataatactat ttgacctcaa agtgaatttt attgttccac acaagcaaca 60

gattacacca atttcacaac tcccagaatc caaacctaca aagacccttc ccaccaagca 120

ctttaccaaa aacgggcttc atctccatct tcctttcttt cacagttgaa aaactgccct 180

tcctaattaa gccaaccaac ttcttacctc aataaaatcc ttgtttttca gtagcatgta 240

cagtatttcc agtgatgaac agtgaactgt ctttcgtctc acacagtaac ctccgtgaag 300

aagatccacc ttgttcttta ctgtatattc ctggcatgct aactgcatcc tcagacaatt 360

ttaagtgact gaaaactcag gcaaagaaag gcaagagggc aaatagaagg gcacaggaga 420

caacgctttt caaatttttc tcactgcgac ctacagaaac acactgtaga acacctccta 480

gtacactcac acgtgtgtgt acacctgaag tgtcaagaaa caatacccta agtgcaacac 540

cctctgatat tttctatttc aagtggccgt gatctactaa actgatttcc aactcaccaa 600

taggattcag tttgaaaaac actgcaataa atcaaacctt acagttgcat tccacaagct 660

actaatgaac tcttgaaaat ccagcataca gcagagacgc tgaccaacta caagatccaa 720

acccccccagg tgggcagtgt ccttctgttc agcagtggca gttccccacc accaccagcc 780

ctgagagtta attatctccc aaactcccag agtttcccaa gtagcctgag gtgtctgtca 840

tatgcccttt taacctcttt ataaattcag tcccgtccgt ctcttacggt ggcaaagttc 900

atttatcgtc ggctgtggaa agcaatacnt tctttttgtc cccttcagga acccagaatt 960

aatgaccagg ttggtgcccg gtgtgccttt atgatcta 998

<210> 16
<211> 797
<212> DNA
<213> Homo sapiens 2.D.48

<220>
<221> n
<222> (1)..(797)
<223> a or g or c or t

<400> 16
gcccctctga gttacgggga gccctgcaga cacccagccc ctggggatcc tctccccgac 60

ctgcccttcc cctccgacac ttgccagtac tccccggcct ggtattcctt tcgagacccc 120

ctcacctatt ccaggctgtc ctccactgag gcgaagctct atgaagtagc ccaatttcaa 180

tataattcac gttgtgtaaa agaactttga agacggacta catcgtgcaa ggacaccgtc 240

acccgaaaac cattggtgga acgttaaaac aaacaaaaaa caaaacggca aaacctttt 300

gaaggcaatt ttgacattta tgaatttaca gttattattc ggtttgtccc tgaaatgtca 360

cttctgaaaa tttgcatagt tttcattatc actaaaataa tctagtaaat attcccgaat 420

gaatgcattc aagaatattc actaaattat tttagtgata aggaaaaagt ggaaatagct 480

gacagtcatc aatttataaa taaaatgatg gttaaataaa atgatgaaca ttcatataaa 540

ggaatactct atattcagac gagatctgtg tgctcacagg caaacaggtc taagcttact 600

ttaaatgaaa aaggataaat tgcaaaaaga atagtttgtg taatatgatt ccacatttgt 660

aaaaatggag aaagaaatng taagcanatg tctgcaagca atcagatatg attagtgact 720

taatttcatg gatagttata taggaaatat atgtatattt tatatgcaca tagatatgga 780

ggaatatact ttcactg 797

<210> 17
<211> 1024
<212> DNA
<213> Homo sapiens 2.D.55

<220>
<221> n
<222> (1)..(1024)
<223> a or g or c or t

<400> 17
gcggccgcgg cgctgcacgg gcgtgacgtc atggcgccgc ggagccgcgt cctccccgcc 60

ccgccccccgg ccggggtcac ccacccgctg ccggggctga cagagaccct ggcccgcggt 120

ctgcagcctc ctcagtcgtg cgtgcgttca ttccgctcat agcttctgtc actcagcaag 180

cgctcaacac agacgcatga gataccctgg ctggaaggcc ctgaaaggta gtcgtccatt 240

caacacgtgc ttagcgcgct gctgatctgt gccaggcact gggccagggc cccgacacgc 300

gtcagggtag aagcaagcag aagcctggcc ctgttggagc ttacattggt aaataaccaa 360

gataatttca ggtaaatatt aggtcctatt aaaaatatgc gtcttcgcca ggcgcggtgg 420

atcacgcctg taatctcagc actttgagag gtcgagcacg ggcggatctc ctgaggtcaa 480

gagttcgaga ccaacctgng taaatggtga aaccgcatct ctacaaacat acaaaaaaaa 540

aaattagcag tgagctgtga gcttgcacca ctgcactcca gtctgggcaa caggacgaga 600

tcttctaaca acaacaaaaa aaaagtatgg gccacctagt ccagccaaaa aaacaaagtg 660

ctttttttttt gctttttttt ttttttttttt tttttgagat ggagtctcgc tgtgtcgccc 720

aggctggagt gcaggggcgc gatctcagct cactggaagc tccacctncc gggtttacgc 780

cattctcctg gctcagcctc ccgagtagct gggactacag gcacatgcca ccatgcctgg 840

ctaatnnttt gatttttttgg ttgggtgttt agtagagacg ggttcatcgt gtagccagat 900

ggctaactct gactgtgatc tgcacttgcc tccagtgtgg atacagggga ccacttgcag 960

caaagctcta ttcctgtagg aggggtgttg tgaatcagac ccaatttgga aatcaaattc 1020

tagt 1024

<210> 18
<211> 1854
<212> DNA
<213> Homo sapiens 2.D.74

<220>

<221> n
<222> (1)..(1854)
<223> a or g or c or t

<400> 18
gcggccgctg cagaccctgc tccaggcgcc gtagccttgc aggaagagca gacaaagaca 60

ggagagaggc aaagcgccgc ttgcccagag atgcagtcgg ctcagtcaat agagggaaat 120

cgcctccaaa cccaggctgg gaatgaggga ggaggggcga ggcggctggg gactagaaaa 180

agcagcaggg aattaacgtg acagtcagag cccagccagt gcctcgccgg cgctgctctc 240

tcgcctcgcg gttgcggngt ccggaatgga gagaggaggc gggggctgag ccgttggctg 300

ccggagacca gctgaggtag gagtattaac tccctctgct gctctcgcct gccttcctcg 360

caccccctta cacagctcta cttgcagcag gctatggccc cattctttct cctatttttc 420

taactactga gatcagagct gaattaagct ggtgaaagga gcaaaacgtg caagggattg 480

attgccctcc ttgggggaaa agcggaggct taaaatcaat tcgacaaatg agtgtttact 540

gggtgctgag tactgtgctc cgctattgtg agggagggtt atgaataagg tacccccctc 600

ccgccccagg gtccgttgtc agatctcaga atcagtttcc cctgcagttc tggaagccca 660

aagtttcggg gttgagttgt ggtccctgat cccgatcctc aaccaatcta gctttctaaa 720

tcagaagaag gtggaattca attttccttt ctccttcctg ggatgacttt aacctgcagc 780

cgaaatggag tctataggcc ccttaaaaaa gcgcgcgcac gccagtgtgt gtgtgtgcga 840

gcgcgctcgc gtgcgcgcgt gtgttttaag agtaagtcaa attaatggtt ttagtgatgt 900

tcttatttca tgattttaat tatttaccat atctgcagta gacaccagtt tggggcagag 960

gaacccgcct ctccagactc tacaaatacc acctttttt ctaaagcttt tttccgctac 1020

cccagtcctc tgactcgagg cagaaatctt tcccctctct ttgccctctc agaattttat 1080

ttgccaatca cttgcggaac ttatatattt atagatttat ctcttcactc acatatgagt 1140

attccctgtg ctttttgttt gtttgttctc actgcaacat ccagcagtgt tttgtatcta 1200

atgggtactc aaggaaagct tatccagttg aaggtcattt tctccttctg tatgagctaa 1260

atctcagtgt ctctagaatt aaagagactc cagggatgga acttttgatt tagggtgtgg 1320

tgaagggacc cacacataca gttagactca cagccccttt actggaaagg taataaagta 1380

tttaattcat tttggtctct agacaatcaa ccttctccca ctgaccaccc acctctgttt 1440

cctgaattcc caaaagcaaa agaaaaccaa actgctaagc aactgcctag agcaagacat 1500

gtatgttcag ctgccaacac ctagagcaaa cccattccaa gtggagaatg accaaaaaat 1560

cttgattatt tcttgacctg tgtcaagtat gttgaaagcc tgccaaagtt tcctcatttc 1620

tattgaagca ctcttattct ggatgcattt tagaacagtt tgaacagtgt tacattgctc 1680

agaggtgaag aaaattgctt tgtagtttaa ggatatttaa gatttgtttg tttgtttgtt 1740

tgttttctgt cccaccttct acaaattgca cgatagatac ctcagatcag gaatgctgca 1800

tgaaaaagta tgtccataat gcaggagatt agactaaatg actcttaaga tatc 1854

<210> 19
<211> 674
<212> DNA
<213> Homo sapiens 2.E.20

<400> 19
gcggccgcct tcccttccca ttcactggct gcctcctttg tgaactaatg actgtaatta 60

ttacctccca gagctctttt gttatctcca accccaagcc ccggagaggg ggaatgggct 120

ctttagtgaa atgaaagtca ttacaaagca aattaccgtc tagggaggga cagccttcag 180

gaaagacaaa tcagatctcc atctgcatct gaagtagggt gtgtttaaat aaaaaatgta 240

aatatcacca ttagatccaa agtactccag agctgtggga tttaatggag tttaaacggt 300

agcacttgaa gccattgctt taccaaaaag aaaaaaaaat cagttaaatt caggtgtttt 360

aatccgtttc ttctttgggg gttttgtgtg atttaaacgc ttgcttttaa gaacctttat 420

gttttcaacc actcatccat agtagaaaag ttctgcaacc ctagactgct ggcttgaagg 480

aaaacctttg caggatttga tatggatttc aacaaagaac cagcctctgc gaggctggag 540

agagctgcgg agctgccatg cctgaagtgc agatggctga accacaagtc tttaggtttc 600

cggagttgtt attgtggtga cctagagtgt cagagccagg agagcaagaa agaggagcca 660

aactgagccc tgag 674

<210> 20
<211> 676
<212> DNA
<213> Homo sapiens 2.E.24

<220>
<221> n
<222> (1)..(676)
<223> a or g or c or t

<400> 20
gcggccgcag acgcgccagg cccgccaggg cgccgcacgc cgggcgcgcc acgatgtcca 60

cgaagcccac gatggacagc aggaaggcgg cgtcggtgtc gggcacgccc gcgtccttgg 120

cgtagttcac cagcaggatg gcggggacga agagcccgag cgccatcagg aacttggtga 180

cggcgtacac ggcgaaggcg cggtcggtgc acactgccaa gtccagcagg cgccggcggg 240

gccggaccct gggggatgcc tcgcgcagct gcagccccgc accgtcagcc tccgcctcgc 300

ccggagcgtc cccggcgcgg tcgccggcgc tgtccctgcg cggtcgcggg cccggcccgg 360

gcggcggcct catgacagcc ccgcaggcgc agcagtgcag caggagcccg ccgagcagca 420

ggaagccgcc gcgccagccg aagcgctcca gcagctgctg gccgagcggc gacagcgcgg 480

acaggaacac ggngctgccc gccgncgnca gcccgttggc cagaggccgc cgncgctcga 540

agtacagccc cagcatgatg agcgacggct ggaagttgag ggccaggccc aggcctgcgg 600

gcgaggcggt gctgtgccgg ggtccccgga gagcccctcc ttgggcccca caggagggag 660

gggccaggcc ccggaa 676

<210> 21
<211> 455
<212> DNA
<213> Homo sapiens 2.E.25

<400> 21
gcggccgcgg ctgggggcgg ggaggggggc gcaggacccc aagtgggggt cccggagcca 60

gaggcaagtg tcctggggtg ctgggggcgc cgtgccggcc gggccgctgc cctggcctag 120

gctggtccgg gggctagcgc gccgggggct gcggccgatg ggcggggcga ggggccgcgg 180

gggtggcgag ccgggggggc acgggggtcg ggggtgcccg agggggcgcg gccgggcggg 240

ggtggccagg gatgggggtc actgggggca aaggggatcc agtggggggg tcccgatgga 300

ggcgtgcagg gccaggggcg cccgaggcgt gcgggggtcg ggtgccccag actggtggcg 360

tcagacaggc gtgggtcgtt gggggcctgg gtcgcggctt gactgagggc ccggccgggg 420

ctgtggggcg tcaggagagc gtggggtgtt atggg 455

<210> 22
<211> 156
<212> DNA
<213> Homo sapiens 2.E.30

<400> 22
gcggccgcgc ttcgacgacg acgacgactc cttgcaggag gccgccgtag tggccgccgc 60

cagcctctcg gccgcagccg ccagcctctc tgtggctgct gcttcgggcg gcgcggggac 120

tggtgggggc ggcgctgggg gtggctgtgt ggccgg 156

<210> 23
<211> 978
<212> DNA
<213> Homo sapiens 2.E.37

<220>
<221> n
<222> (1)..(978)
<223> a or g or c or t

<400> 23
gcggccgcta cagtgcgtca acaggcgctg taatccgagc gcataaacga ggggtccggg 60

ggtgggggcc cggggcggcc gtggcagtgg cccggggctg gcagcccgct ttgaaaatct 120

ggcgaagtcg gggagcctgc gtttgctttg gcagctgcga aggcgcacag gtgcacgggg 180

gcgggggget ggctggcggc gccaccaccg accgtcactg acagagcctc gccatgggcg 240

cccaaattcg ttcacttgcg aattgcgtaa gcggccctcc ggtacccaac ctctgggaat 300

tacgcgggct tgtgcctgtg gccaccttgc taggccccac cgctccagcc tgaactccca 360

ccgctccctg ccttgcgctt gatgttccag caacttcgaa ctgtttttat ctcctgtaaa 420

ccaagccgct tctctccttg acgctggcct tcctgcctgg cttgccctcc cgccttcttt 480

tgccttttaa gaccgggcag ctatcccacc ccgccagtat atgcccctct tctgggctcc 540

ttggcttcct gtttatacct acgtgactgt gcttactttt ttgcacatgg tttttcttat 600

ccttctgtaa gtttcttgaa ggtaggagcc atgtcttacc ctgccaagca cattgtctgg 660

cacgtagtag ctgttcagta gaggaagtgg tccctttccc taaagggctt tncgtctcac 720

tggagagaaa ggctagcctg gtaccaggga ctgccgagat caagtgatgg cagtacgtgc 780

gattcgatgg tgccgaaagt gacctagaga ggcagctgng agtgctctgg tgctcgcgga 840

tagagctttg gcgatattgt catttacaat gaggactgta ctctgagacg tggaccttct 900

aacagaccat tataaccttt gctctggagg agtgagcnag caacggactc tgacancatg 960

ttttgacaat gggtattg 978

<210> 24
<211> 321
<212> DNA
<213> Homo sapiens 2.E.4

<400> 24
gcggccgcac cggctcgggc tctgccaagg gacccggcct gccccaatgc cgccggcggg 60

cggtgcccgg tcgaccctgc acctgactgc gaggcgcggg aaatgaccgg gtctgtcagc 120

ctcccatcgc ggcttccgtc tacaggtact acctgtgctc tgtccagcct cagccactgg 180

acgatccttc ccgtagccgt aggaaggggc ggcgcttcct tggaggggat attagaggcc 240

cgaattcgcc cgggaagcgg cgggagggcg ggggtgccgg gaaggaggga ggggagaagg 300

agtgagggaa gtgggtgtat g 321

<210> 25
<211> 1023
<212> DNA
<213> Homo sapiens 2.E.40

<220>
<221> n
<222> (1)..(1023)
<223> a or g or c or t

<400> 25
gcggccgcgg gctgggggcg agcgcacacc ccgcgccgct ggagttcact gccgggcgcc 60

ggcatgggcc tgggggaggg gtgcacaggg cccggagggt gcgtgggtgt ggggtgcgcc 120

cggaggagag cgaggctgcc agagtgcgtg tgccgactga gccagtgtga gtgtgcaggg 180

gctggcggag agactgggag cgagtgtgtg tgcatctaac cgggaggttg tgagtttgtg 240

tgcgcgcacg cccgcagaga agttgtgagc ctgtgtgtgc acctaacaca gaggttctaa 300

gtgtgtgcac ttgtatgtgt gtgtgcacac gcggacagag tgattgtaag gatatgtgtg 360

cacctcacag agaggttgtg agattgtaag ggtttgcgca cctaacggag atgttgtgag 420

tgctttttt cctgacaggc tgtgagtttg tgttgtgtgt attagaggtt tgtatggacc 480

tgactgaggg gttgtggaat gtgtgtgcgt gagcatgagc ctggagaggt tctatgcctg 540

ttcactcctg acagagtttg tgagtgtgta tgattgtgtg actacaccac ccaactggcg 600

gattgaatgt gttgtataca tctactgnga gggcgtgtgt gtgtgtaaat tgtatacaat 660

gaggctgtgt gcatcagtgc acctaaccac gaacctgtgt gtacagatgt gtgtgccttt 720

ctgtgtatca gacatgaggc catgtgtctg ngtgtgttta gttggttgtg caagtgctgg 780

agtctggggg ggagagaggc agttcggagc cttcccgctt tctccttctn cactctntgc 840

ttgtctcggc caccagcatg ttggaggact acaaggctgc ccttcaggcc ctttagaccc 900

gcttaaggca cttgtgatcc tatatgccag atgccctccc aaagtgccag gctaccacat 960

ggcttggctg attgattggc attgaccacc catttgttct ttgcttcctg ggcgggtcat 1020

aaa 1023

<210> 26
<211> 964
<212> DNA
<213> Homo sapiens 2.E.61

<400> 26
agccacatgt gtacccatct tcctcctctg tggaaggcgg aaggaaacag atgccctcca 60

aatatggaca gctgaaatga tgaagtgctg aagccctggc ccagaccctc agagagatgt 120

actcaaccac ctccccaccc ttggacaagc acaaaaccag agaaaacaaa ggccagcaac 180

tgtggctcag cccgcataaa tttcttctgg acactggcct gtctatttga atatctgtaa 240

tgtttggtgg agtcaggggt gagggtctca gcctttggct gctgcatctc cagacaccaa 300

tcatggggtt cttttctttt ttttaatttt ttttttttgt ttggaaccgg attccaaggg 360

gccaatttaa gttaacttcg gcttccaagg ttcaaggcaa ttcttctggc ttaaccttcc 420

aaagtggctg ggaataccag gattgcacma cmatgccsgg ytaatttkgw attttwagka 480

raracarggt ttytccatgt kggtwaggyt ggyctmaaac tytsgacctm aggwgatcca 540

cccgcytsgg cctccmaaag tgctggratt acagsswtga sccaccgkgc csggcccatc 600

atggtcttac taatgggtat tttcccctta acatgtcatt tgagcccctg cctgctcatc 660

agtaaactgg gctaattaat aataccctcc tgtagggctg ttgtaagaat aaaatggact 720

atttgagaaa agggcttaac aacagggtat agtgacagag gactcggtaa ctgctttttt 780

gtgcttatta agagagaata ctacagcaac ctatgggaag atttggagtc acgaaaacct 840

gttctccgtc cttggagcca cagctggact acatttccca gccttccttg cagctgggca 900

tggtcacatg actgtgctcc agccaatgga atgtgaatgc aagtgatatc aagcttatcg 960

atac 964

<210> 27
<211> 748
<212> DNA
<213> Homo sapiens 2.E.64

<400> 27
gcggccgctc cgttgactgc agggccccgg cggtcttcct ccgctgttcc gaggccgttg 60

agggctgatg tgctccatcc tcccacttgt ggtttggcaa gccatccagc cgactacaaa 120

cccacgtttg tgagttacct gctggctgtg acgcttccgt caaatctgag taacagtttc 180

ctcatctcta agatgggtaa catagtatct acctcacagg atcgtgtggg cagtacatgc 240

atagaaagga tttaacacgc agtgtactca gctagtttta ttatttatcc gtaatgatca 300

tttgttcttt tcccctaact gtgcctcaca agcatgaaac agaatccacc aaacatttag 360

gtctgggtag tggttggatg gaaacccatc gcgggttaac gcttccaaca ccagtccctt 420

gacactctcc cgccgaggag gctgatttgt aaacttgctg agaagagaat acccagcaga 480

tctttcaggt ttcaaatcca cgttctttac aagttgtgtt aattgtttgt atatgctttc 540

gatatagagt ctctaggaag taatactagt acatgtttta aaattcaaat actgccaaac 600

agtgagatgt aagtctccct cctaacttct gtttcccaaa tcccatgtcg tttcttctga 660

tgcaatagac attgtatgtg tgtgtgtcta gatagataca tatgtgtatc tctcggcttt 720

ttttttttct tttaaagagt aaaccaag 748

<210> 28
<211> 250
<212> DNA
<213> Homo sapiens 2.F.2

<400> 28
gcggccgccg gggaagggcc ctggaagagc aggaccaggc agagcgggcg ctggggtctg 60

cgctggagct tgcgctgagg ccggggtctg gccaggagcc gcagttgcag ccgctgctgc 120

cgcagggtct gaggatgagg ctggagccgc agcgggaacc ggagccgcag ccggtgctgg 180

cgttggcgct ggaactgagg ctggggccgc cgccgggact ggggttggcg tggccggagg 240

agcacttact 250

<210> 29
<211> 657
<212> DNA
<213> Homo sapiens 2.F.41

<400> 29
gcggccgcgt acggacagcc agtgcattag gcagggctcc cctacgcgcc cggagagcgc 60

ggaccgctgc ctcgggccgg cgccgcctcc tgccgcctgc cgccgctcgc ggagcccgag 120

ccccagcccg agccgccgcc taccccaggc cggggcgtcg agcagccggc ggcctgtcca 180

tgtggggcta gccctcgcgc ctggcctgca tcaggaccag caacatggag gcggccgttt 240

gcgaccccga cacgcgagga ccagggcggt gcggagcccc gcgaggacgc gacgcccatg 300

gacgcctgtc tgcggaaact gggcttgtat tggaaactgg tcgacaagga cgggtcgtgc 360

ctgtttctgg cccgggcgga gcaggtattg cactctcagt ttcgccatgt ggaagtcaga 420

atggcctgta ttcactcgct tcgagagaac agagagaaac ttgaagcgat tatagaacga 480

ccatttgaag gaattttaaa gcgcttcgga aattcacagg aatgggtatg acaaatggaa 540

aaaagagccc tttctcttat gtacaggaaa gattttattc ctaaactgga gccaaaggtt 600

ctttctcaca agtaactgaa aatattttcc tgaaaggggt tactggtgtt tttaaat 657

<210> 30
<211> 318
<212> DNA
<213> Homo sapiens 2.F.50

<220>
<221> n
<222> (1)..(318)
<223> a or g or c or t

<400> 30
gcggccgcgg agcgattgca tgcaggggcc gcgtaccgng aagtgcagaa gctgatgcac 60

cacgagtggc tgggcgcggg cgcnggccac cccgtgggcc tagcgcaccc ccagtggcta 120

cccacgggag gaggcggcgg cggcgattgg gccggcggcc cgcacctaga acacggcaag 180

gcaggcggng gcggcaccgg ccgagccgac gacggcggcg gcngcggagg tttccacgcg 240

cgcctggtgc accagngggn ntgcccacgc ggtcgcagna tgggcgcagg gcaatnncaa 300

aacancactt gggcccng 318

<210> 31
<211> 525
<212> DNA
<213> Homo sapiens 2.F.59

<400> 31
gcggccgcct cccgccagga agggtggcgg gcccggaagg ccagagatgc cccagtgctt 60

cccgcgccgc tacgcaccta gctgcccgcg ggtcccacat ggctgcggcc ggagggtccg 120

caccaggacc gccgccgcct ggggaagcgc ttccctgtgg gcagggcgcg gcgggcagtg 180

cggaagcccg aaagctaccg gagcccgggg caggggcggc gcgatgcaga ggcggcgttc 240

gggggccccc agctgcctgc ggctcggcta cccagccgcg atcagagggg gcgggggacg 300

caggaacccc ggcgtccggg cggtgtgcag ccgcagacct attccaagtt tccacgtagt 360

tgcgagagcc caaaaactgt cacgtgcacg tcgctgctga gtgggaggag gtgtttgtca 420

tcgcgttcaa aaggggcgtt tcggtgtctc ccgtcatgca agcaaatggt atggctctcg 480

gccgcctttg aataaacgag tgcttcgaac cctttaccag gaggg 525

<210> 32
<211> 1032
<212> DNA
<213> Homo sapiens 2.F.70

<220>
<221> n
<222> (1)..(1032)
<223> a or g or c or t

<400> 32
gcggccgcgg ccgggggggct gagaagggcc tgggtgcctg tcgcccggga gccgaggttt 60

cccggcctcc cccgaccccg ggcgccaaga gcagtcggtc cccccggcct cccgccggca 120

aaggggccct ggggcccagg cgcgcggccc ctgcgtggcg gcaggcggcc caggccagcg 180

ccggcggcta gagaaggcct ccagtccagg cctcatggaa gggcctgcct cgagcggccc 240

ctcaacgccc cgcagtgtgg cactggaagg gacctaaaaa cccacctggc tttctccttt 300

ccccttcccc acgcttccca gggcccaatg cccgcatctc agtttcgctt tccggcaggg 360

tcaggggtga gagggaggaa ttctcaggtg tcacctcctc acccgcctgg aggcggaggc 420

tagaaagacg tcggggcact ctggagggga ggaagaggtg tgcctagaat tctctctctt 480

aaacgctcgc gttatcacgg aggagacttt ataaacactt taaacacaac accaaccatt 540

ttatcagcaa aagcgagggg agggggcgt acagtaaatg ctgagagatg ttcgagaagc 600

cccaagacgt tccctgcgga aggagaacgg aagaaagaaa ttacgggcgg aaaaagagta 660

aatattagct ccacacctaa ccacttncnc agccccaaac taggagagaa tctgctaaga 720

ttcgctttat atttatatag tctatgtgat gttaacaata ggggttgcaa atattgcatg 780

ggggcattct tagagtaaaa aattggtatc tacctgaaat tcaaaaattt aactgggcat 840

cctgtatttt tattggctaa tcctgcaatt ctaactaaaa aacancttgt gaagaaatca 900

tatagaagga agctaattgc tgatgaatac agtattggga actgttatgg aactggctgg 960

aaagaaatga ttctctacga tactttgagc catgtaggtg agagagatga tgagcactgg 1020

atgtctacta tt 1032

<210> 33
<211> 708
<212> DNA
<213> Homo sapiens 2.G.10

<400> 33
gcggccgcgc ccaggcgccc cttcccctgt ggggcaaccc aagccgggga cgcgtgaacc 60

acctccgtag ccgccccgcc agcaccccca gccgtgcgcc cctgcaccac gcagctgccc 120

tgcgcatgga gcccagaggg acagcaggcc cggcccccag caccaccggc ctgccgggag 180

gttcgggaaa ctggcgtcgc agcggagagg gcatcaggcc aacgcctccc ccgaggctca 240

gctgcgggct cccaggcgta ggcacccacg gcccttacgc tgaccgtagc ttggacgccg 300

ctgccgccgg ggtccaatgc cggtcatgcc catcccgcgg gggttgtgct ccttccatgg 360

tccacacacc acctgcctgc atgcggtctg tgggcccgtg ggcgcctccc acctggcccg 420

caccaagtac aacagcttcg aggtgtgcat caagacgcgc tggctgtagg gcttcatcca 480

cttcctgctc tacttcagct gcagcctgtc actggggcac gctggccgcc ttcttctgcc 540

tgcagtactt gggcgttagc gtcctcctgt gcttccaaca caagctgtgg gtgctgctgc 600

tgctgcttgg cccgctggcg cgttgaaatt tcgctgttga acgagctgct catctacagc 660

atccacgtca acatgcttgt tgtatggggg cctgggctgg atgcctaa 708

<210> 34
<211> 569
<212> DNA
<213> Homo sapiens 2.G.108

<400> 34
gcggccgcac acgtgtccag gcgtcacgtc cgcgcgcgcc cccggggctt gcgtcagcgg 60

ctgttccaga agcgggtggg ccagggctct gcgcaccgct ggggttcggg gcccgggacg 120

ccgccgggag gagggcaccg cgcggggtcc gacgcggagg cgtgctcgga acgccggggg 180

ctgcggagtg catcagcgcg gtccagccct ccgcctgccg ggcgccgagc gtctccgccg 240

cccggacctg ggctgggcgc cgtggcgttg cctcggagct cgctgcccgc ggggcgcgca 300

ccgccttgac ccgggcggcc ccgcggcagg caggcgcccg cagttccatg gttggttcgg 360

agcgcgatga gccgcccgtc ctccaccggc cccagcgcta ataaaccctg cagcaagcag 420

ccgccgccgc agccccagca cactccgtcc ccggctgcgc ccccggccgc cgccaccatc 480

tcggctgcgg gccccggctc gtccgcggtg cccgccgcgg cggcggtgat ctcgggcccc 540

ggcggcggcg gcgggccggc ccggtgtcc 569

<210> 35
<211> 916
<212> DNA
<213> Homo sapiens 3.B.30

<400> 35
gcggccgcgc tgagctcact ccgggccctg cggaaagaat tcgtaccgtt cctgttgaac 60

ttcctgaggg agcagagcag ccgcgtcctc ccgcaggggc ccccgacccc cgccaagacc 120

ccgggcgcct cggcagcctt gccagggagg ccgggaggcc cgccgcgggg tagccgcggg 180

gcgcgcagcc agcttttccc tccgaccgag gccctgagca ccgctgccga ggcccctctg 240

gcccgccgcg ggggcaggag gcggggcccg gggccggccc gcgagcgtgg aggccgcggc 300

ctggaggagg gggtcagcgg ggagagcctg cccggagccg ggggccggag gcttaggggc 360

tctggcagcc ctagccgccc cagcctcacg ctgtctgatc cgccaaacct cagcaacctg 420

gaggagttcc ctcccgtagg ctcggttccc cccggcccta cagggtgaga ctcagctctc 480

atgcaggaga tgggtaccac gaaggctctg gggagtcagt cattcgagct cggcgctccg 540

cagtggagcg ccaggatggg tagaaggctg ggggtgatgg tgagggtttt tgtggggttt 600

cttcgcagcg gccatgctct gccccgtggg ccgtcatttt gtcgtttcgt tttctctata 660

atgtaataac taactaggca aaaagtgtta aaattaataa ctactaaata tccgatgtca 720

ttacaacatt tataatatat aacaatatta aaacatataa ttaataataa aaaaaacctt 780

attttaatct ttttcttttt gttaatttat atcaccttat ataccatttt tctcaatacc 840

attcgataca atcataaatt tatttattgt atattgtcaa aataaaatat tcctctatat 900

aaaaataact ctccta 916

<210> 36
<211> 998
<212> DNA
<213> Homo sapiens 3.B.36

<400> 36

gcggccgcag catggctttc ggccactact cggagcactg gaaggtgcag cggcgcgcag 60

cccacagcat gatgcgcaac ttcttcacgc gccagccgcg cagccgccaa gtcctcgagg 120

gccacgtgct gagcgaggcg cgcgagctgg tggcgctgct ggtgcgcggc agcgcggacg 180

gcgccttcct cgacccgagg ccgctgaccg tcgtggccgt ggccaacgtc atgagtgccg 240

tgtgtttcgg ctgccgctac agccacgacg accccgagtt ccgtgagctg ctcagccaca 300

acgaagagtt cgggcgcacg gtgggcgcgg gcagcctggt ggacgtgatg ccctggctgc 360

agtacttccc caacccggtg cgcaccgttt tccgcgaatt cgagcagctc aaccgcaact 420

tcagcaactt catcctggac aagttcttga ggcactgcga aagccttcgg cccggggccg 480

ccccccgcga catgatggac gcctttatcc tctctgcgga aaagaaggcg gccggggact 540

cgcacggtgg tggcgcgcgg ctggatttgg agaacgtacc ggccactatc actgacatct 600

tcggcgccag ccaggacacc ctgtccaccg cgctgcagtg gctgctccct ctctttcacc 660

aggtaaagcg ctctgggagg cgtgggccag gtcttttctc ctctgaaaar ggcggagtag 720

agacagaata tgctgagttt gcaagcaggg ccccsggttt ggggtttcgc tccaggtccc 780

cacccctcaa aaccaagaat cgcgtcggta arggractca cagtgagggc tgcgacacgc 840

gcacgcgccc cacccagcgg tgccccgaac ccctccggtc yyctatctkg yytctatcgt 900

cccctcmcyt gcttkcgagt gagaacacat ttgcaaagac ccctccaccc cccggaaaaa 960

caagagtttt taaatgcttg gagatgagcc ctgatatc 998

<210> 37
<211> 514
<212> DNA
<213> Homo sapiens 3.B.55

<400> 37
gcggccgcgg cgctgttggg ccagcagggc agcaccgagc ccgacttggt gccgcagtac 60

tgcgggggac tgcgggcgcc ccagcccgac gggtcggcgt agtagccgag cgggcggcca 120

gtgcagcctg cagcctgcag cggcagcgcc ttcacgcccg ccgccgcgta agagagcagc 180

gtggccgcgt tgcccgcgaa gtccgtggcc gtgtcatagg ccgaggccgc gaagtccagc 240

cggttgttgg ccggcgtcac aaaccagcgt tgcggcgagg gcgcgcccgg gtcctcggcc 300

tgctgcggcg acagcagccc gttggtgtgc ggcacgctgc ggtccgtacc cggcccgggg 360

cccgcgcccg cgcccgggtg gaagcgggcc ttggcgtagt tgctcacgaa ctggtcctgc 420

aggaaagagc cggccatggc gtagcgggcc ccgggcacga tctgcgagcg cggcgagtcg 480

ttgggcgagg gggtcaggcg gtccatgtca cagc 514

<210> 38

<211> 608
<212> DNA
<213> Homo sapiens 3.C.01

<400> 38
gcggccgcgg cgcagcggag gggctgcggg cccggaaccc aggccggtca gcgtgtaagc 60

gccccagccg gccgggctcc gtgggggggtc agctccctga cccctacagc gcggtagcgc 120

ctctccgaga gctccgggac cagcggcccg gccgccccca aagccagcct ccctctccct 180

tccccgcacc gggatcccag accagggagg gggcgcacgt ccgacggctg aggaatagca 240

gggcgcgagc cggcccggca ggtgcccatc gtcgccctct gggaccccgg tggcgcgctc 300

tgtcctccgc gccacgctca gccaccaccc cggctgtttg ggacccggca cccagccgag 360

cgcgccgccc cctcggggac ccgctgggcg gggctgagcg aggcttggag tgcgggcgaa 420

gggacgtggg gcgaacccgg ggcgctgcgc cacctcggct gtctccagcg gagaccggcg 480

ccctcgcccc ccgtctccgt tcattgtgct gtattcatcc agcagatttt gaaacaattc 540

tcgtgtaaaa aggcatttta ctccgcgcgt cttccttaca gccatttagt tgggagtttg 600

cggtgggc 608

<210> 39
<211> 1025
<212> DNA
<213> Homo sapiens 3.C.16

<400> 39
gatatcctcg ctgggcgccg ggggctgcag ctcgctctgc tgctgctgct ggtagaagtt 60

ctcctcctcg tcgcagtaga aatmcgsctg caccgagtcg tagtcgaggt catagttcct 120

gttggtgaag ctaacgttga ggggcatcgt cgcgggaggc tgctggagcg gggcacacaa 180

agcgggaggc agtcttgagt taaaggggtc ttggtgcgra aacctggcgc agcgcgcagt 240

gcgcgccaca gtcccgaacc tctccccttg cagagctatc ccctaaagcg gctgggtggt 300

cttggtgggg gaataaaggg agcacccttt cacccccttt ggacagtccc ctgctatctc 360

ggagacgcac ttagtgaacc agcggcttgg tgcccgccga gcccccgctc ccccgggagc 420

ccggagcgca aagcccggga gtcggccccg cagcggcaga ggaatcgaaa tcggccctgg 480

cgcccttaag aagccgcggg aggtggcggt gaggaaaaca atttgccaaa atccaaggca 540

caaagttttg cgccacctga aggagaaggc gagaggcgcc tgggcgctag cggctgcgtg 600

aaccccgctc cgcgccgggg cccctccgct gcggctgttc ccactcgcgc cctagccgct 660

ctcctacccc cgccggcacc gcagcccctc ccaaccttcc ytytccaccg scccgtccc 720

caccccagt accgcccccg tccaacactc cttttgccag cttttcttct ttctctcgcc 780

ggctggagtg gcgagctcag ccgcgggctt taacacccct ccataaatac arggggggtg 840

tcaaataata ataggggcac ctcccttcgc actcaatacg gagatgcaac tgcgccagag 900

accccgctgc gatacctccc ccggagccac cccaccaagg gtagcagctg ttctggaacc 960

gcccagagcc ccgctcctcg cagttcctyc gcatctcggg cgcgaggaca cccgagggcg 1020

gccgc 1025

<210> 40
<211> 1010
<212> DNA
<213> Homo sapiens 3.C.17

<220>
<221> n
<222> (1)..(1010)
<223> a or g or c or t

<400> 40
gcggccgcgg accgacttcc ttcgccggcc accggaggga gggggcgccc ctaccccggg 60

aggggggctgg gcgagccggg agacggtcaa gttggggtcg ggggagcgcg ggcgctccgc 120

actctggggc acgcggggac gagcccggcc gcattgtctg cgcggcctcg gaacaagcac 180

ggccggcggt ggcaccggcg ggcgcgggga ggagttgccg tccccctttcg ccgccgccgc 240

ccaccgcgtt ctttgtgtgt ctctcgccgc cctccagccg cttcgccgct cgcctgacag 300

ctgatgggct caccgcgccg ggtcccgcgt cctctcggcc gcagccggcg gagcccggcc 360

cggcaggagg aggaggggag aagaggagcg ttgacagatg ctgtcttgga gcgggcaccg 420

ccgggggaaa agtctggact gcctcggcga gaagcggccg gtaggcaacc ggccccagcc 480

tcgcattcgc ctcaaagacc ccaattggct aggagccctt ccctccgcag cggctcgcgc 540

agctccgctc ttgcgccccg cgcccggctc agcggacgga ctagcgcgcc cggtcaagaa 600

tcctggggaa cccgctccgc cccctggctc cagcgccctc caatggatgt cggcgtacag 660

aggggctgtt ccgcccaatc aggtgtcggg aagcccagcc agtccccggg gagtgtagcc 720

aatagaaggc gacttcggca cacacccgcc ctgatccact aggacaaacc gctcgagccg 780

gggtggtgga ccgatcctga ggcagatcag ccagtccgcc aaactgtgng caagtagatc 840

tgagacggtc cgtgttaatg actatatcta agagntggat gggaacgggg cgcccaattt 900

tccctngtat acgcttttgg caagttgggt tgaaaactga caacctgagc tgttaatgag 960

gcttctttaa ctgtttatgc tatacgccta gtggctcaga caacgttttt 1010

<210> 41
<211> 413
<212> DNA
<213> Homo sapiens 3.C.30

<400> 41
gcggccgccg taaagcgcgg atgcgcggcg tggccacgcc ccttcagtgc ttgtgacgca 60

ggcgccctgg gctttttggg cgcgaaaaag aagcagtcct gggttgtacc cggcgcagct 120

gggagcggct gcttcctccg gggtcgtatc tccgcccggc atggggctgc tggacctttg 180

cgaggaagtg ttcggcaccg ccgaccttta ccgggtgctg ggcgtgcgac gcgaggcctc 240

cgacggcgag gtccgacgag gctaccacaa ggtgtccctg caggtacacc cggaccgggt 300

gggtgagggc gacaaggagg acgccacccg ccgcttccag gtatgcaggg acccgccccg 360

aagacgaccg gctgcgcggg cctcccccta gacttttggc taccgggccc cgc 413

<210> 42
<211> 927
<212> DNA
<213> Homo sapiens 3.C.35

<220>
<221> n
<222> (1)..(927)
<223> a or g or c or t

<400> 42
gcggccgccg ctccttgcct gaccgcttgc tccccgcccg cccgcccgcc gggttgtcgg 60

cgcggggcca ctggcgggtc gtgatgagca ctcgctcgcg cccccgcacg cacacgcgaa 120

acccggcccg gcccgccgcg ccgccccgcc tctcgcactc ccggagctcg cccaccggcc 180

gcgctggctc acactctccc tcacagcacg ccggccgagg gaggaagggg gcggtccggg 240

ctcccgaggc gtggggaggg ctgtttattt tgggggggagg aggggcgcga ggcaggaacg 300

agctgactgg ccgggatcct ccgacccgcc actgtggcag caccgggaag gcggggagag 360

agaaagaggg agggagggag ggaccgggat gtagaactcc agcccgcgcg ggaggctacg 420

gcgaggggggg cggtggcggc ccgcgggggg ggcggtgcca ggccccctcg gcaatctccg 480

tagtctcctc gctggctgcc cgagggaggc cgggaagcga tcggggaagc tcgggaatct 540

ccggcacggg cctgggattg tcctggaggc acagcgcggc tggagtgcgg ggcancgcgg 600

gggggggcggg gtctgtctcc tttctgggcg gggccgtatc ctgaagcagg cggggcttga 660

gagacccgaa agccacggag tggctcctgc ttgcggtact agttggacag agtaaagtcc 720

tggagttacc tcgcctgagc accctggttt cccgagaggg aatgggcact ctgtgagagg 780

caagctattt gcctgctttc cctccgcaga agaaaaaagg ctcaattgga aggtggagga 840

tgaagccacc ctctatggtc accccaatct gagagcttta ctttatataa ctacattcta 900

aggagtagta aaatacccga ggtggaa 927

<210> 43
<211> 1365
<212> DNA
<213> Homo sapiens 3.C.64

<400> 43
gcggccgcaa ggaccggctg agarmtgkgg gscsctgtgc tgggggcgsg arggagrcgg 60

ccytraggac tgcscscccc ccacaccggg gcccgggcgg gacacacgcc caacgggacc 120

cctgagcccc caggctgggg accggcaggg gctccgggga ggctggtgag gccaggacgg 180

agccgccycc acgcgtagcc gtgaagcggg aggtacgcgg ccccctggag ctgccccgac 240

tgcagccgag ggcgcgacct gtggtgccaa ccgcctgacc ctgcttggcc gccgccgcct 300

gcgggtctcc agcaggtccc accccacgcg cccgcggggc ccgctccaga ggctcctcca 360

aggccgctgc agaggcgcgg ccaggctccc atttctgcgc atccctggcg ctcagacacg 420

gcctgagccg ggtacccggc gactcccttc ggcctccacc gcctcctggg gagggaccgc 480

gcgctgctcc cacgcgggcc cgggggtctc cgcagccctg gcctgggtgc gtccgtcggg 540

ctgctcggct cggagcaccc cccgccccgc cgccccacca gcgcctytyc ggagcgctca 600

ccccgccccc gactcgtgtt gttgttgcgt gggtttttte tctaattctc cggagttact 660

cttttgttgc caattgtttc tatgcccgga ggccacgctg taaatgagat gttacatctg 720

caccgagcta agtaaacact ttataaatga ataaataagt gaataaataa cgaaatcgtc 780

atctcggggc ggcccggctg ccagggctcc ggccgccggc ctgcgggggt ctgtgtggtc 840

ccgggccctg ccctggggtc ggggaggcgc cgggaggggc cgtttcccag ccgtgtccct 900

accctgaccc catcttcctt cctctcccaa atcatcctcc agactctggg cgtttggtcc 960

ccagatgtcg tgtgggattc gtggcttcca cccaccgctt ctcaaacaaa aacgggttgt 1020

caccgcggct cttaaccctg ggcgagccac ggagcgtttc ttcccgggat cgggatcggg 1080

ccgcggctcg aaccggcatc tgcagaagga agacccggcc ctgtaggccg ccgccgcccc 1140

aggaccggac tggtggcctc tccacgtcgt gtccggaccc gacwcatcgc ctccaacgcs 1200

aacaaacgga agcagcggag cctccgcctc cmasscykgc cyctgyscgs yswgmcmggc 1260

gcattsragt gcwcsakkym sgcycaatym mgagagckct gracktckca aytatcwcgg 1320

actarsrrsr rcawwtkmww argsactcay tgagtaactg atatc 1365

<210> 44
<211> 608
<212> DNA
<213> Homo sapiens 3.D.21

<400> 44
gcggccgcac tgccctggcc gccacgctcc gcgcctgcgc cgcgcacctc aggggcccgc 60

cgagagggcg gggaggtgac gaggtgaggt gggggcaggg agcgggctgc gcgaacgcac 120

cgcacacgcg gcctgggagg gaccaccggc ccgcagcccc gggggaggcc cagcggcccg 180

cgcccctgc cggaggcctt gcgccgccgc agtctccctc tgggccggga agagcccctc 240

ccgagccccg agggcgatcc caccctctag gattactcca cgccaggcgg ccagcgaatt 300

tatcccgccc gcctccaccg ccccttcaag ccctggggaa ctgggagaaa cgtggcgcgc 360

agcggcacct ttcccacgct gctcctcaag ggaaaggacg cgagtggtct tgcccaggtt 420

aggcaaggca gatggcatct cagaccccga agtgtgccag ccgcctgttg gggacagaga 480

ggccgaggac ctcgtcacgg ttttactgag gccacaccag agaaccacct agggctagga 540

tgctgccctc agggcaagag ggtgaaacct gaagactgcg agtcgttgtt gagtttcacc 600

cgattcct 608

<210> 45
<211> 1947
<212> DNA
<213> Homo sapiens 3.D.24

<220>
<221> n
<222> (1)..(1947)
<223> a or g or c or t

<400> 45
gatatcatct attttaaaag acatatgtaa aacccaaccc ttaagaaagg attcctatca 60

ctgttcccca caggcatcct cctcagtctt acacctttcc acccccaaa acaaatcatt 120

cagcatattt atttcatact gtaatatagg aaatagctat tttttagact ttttatatta 180

ttagcactga tcatacaaac atggaataga aattccttat gttttatctg gatttaaggt 240

gatacataat ggaatatatt tctatcaagc cgtacacatt agagataatg aaatcacttg 300

tgttctagtt taaacattat gggaatttca gaactgcaac ataacaaata atcctcggat 360

gaaaactaaa tctctcctct ggtcaggcat ctatgtgcat cagwgatgag aagacaggga 420

ctgtggaagg gaaaacagcg agtcaggaag gactgtggcc acgtccattc cctggtccct 480

caagtaatta aatcctgacc tcctctaccc cagtctgtcc tggggaatgg ccaacactgg 540

cctttcacaa ctgtgtgtta ctagaaatgc aacagaaacc cagctgaatc ccctcctctg 600

cccttctcaa aggaaagatc tgtcccagga ccatttgttc caacattttc aattatgaga 660

actgggaaga taaagttatt tttacattta taaagaaaca catatttatt cacmctcatt 720

wcaagraagg tcaagaatct atmcaaanac caagaggaat ttttaaaatc ccataatwcc 780

accatcaaaa gagccacact tagcatgttg gtccacaggc ttctttagca ccctcttyyg 840

ttggtgtatg cacaaaatgc acaatcacat tctgtctaca ttttataatt tgcctgtttg 900

ttgattamca ctatatattg aacaattttt aagacctgca acatatgttg acaacattac 960

ttccaaacaa tgtatttaca aataaatgca cacacacact atctgtctta tatacaacgt 1020

gtcttacttt ctaattctcc actcttgaag atttaggttt ttccaacttt ttcttaatat 1080

attcaccagg agtcagcaac ttttttccat aaaaggccaa agagtaggcc gggcgcagtg 1140

gctcacgcct gtaatcccag cattttggga ggccaaggcg ggcagatcac gaggtcagga 1200

gatccagacc atgctggcta acacggtgaa accctgtctc tactaaaaac acaaaaaatt 1260

agctgggtgt ggtgagtgtg gcggcggaca cctgtagtcc cagctactcg ggaggctgag 1320

gcaggagaat ggcgtgaacc cgggaggcag aggttgcagt gagccaagat cgcaccactg 1380

cactccagcc tgggcgacag agcaagactc tgtcacaaaa gmaaagaaaa aaaaaaggcc 1440

aaagagtaga tattttaaac tctgcaggcc ataggtttct gttgcaacac tcaactctgc 1500

tgttgcaggg aaagaagcca tacacaattt gtaaatgaat gggcatgact gtgttcttcc 1560

cgacatggtt tgccagcccc tgatgtataa cactacagag gatgctgtta gaatgaaawt 1620

tctttacata tctctgatga tctccttagg actaattact agacatgaca tcatggtagc 1680

tgtgggtcaa agggcatgca tgctctggga tgtacattcc cagattgctc atcatgagcc 1740

tttctcatgt caaaatgttt tgtgaccacc agaaaggctg gttctgcttt tawtacccat 1800

ggawtgagga atagaaatga catggcatgg cccttcccca cagcaccacg gcttctcttc 1860

ctcagcacgg cgacaggggc ttccccttg ccgccgccgc ccgccaagct ccgccgccgc 1920

cggccaagct ccgccgcgcc cgcggcc 1947

<210> 46
<211> 1637
<212> DNA
<213> Homo sapiens 3.D.35

<220>
<221> n
<222> (1)..(1637)
<223> a or g or c or t

<400> 46
gatatcttct gataaagaac caatctgcct gggagtttca aatctgaaaa agcaaatcat 60

agtttactgg agtaaactgc tgtttaaaaa taaaagagaa aggaaaaaaa aaagaatgtt 120

tcctagttcc agaactgaca actagagcct aaataaatac ctggacaagg gtaaatatga 180

cctcaaattt ataaccgccc tgaacgcaga acatcaaccg cgacagctgt ggcatcagcg 240

gcgacagtaa ttttctccct ggcattcaac cagagggcag ttggactgtg caccgactgc 300

actagtggtg ggtagccaaa gctagcctcc aaagtgaacc acggtctggg gcctggtccc 360

gtttgaccga aaatgctatc cagaacmccc wycgagactg caggcccttc ttcctgattg 420

agctagaggt gagtgaagac agggtctggg gtagggaggg gcgtccacgc cagcttgccc 480

attacctgcc ggccttggtg atgatcatct cagtgcctat ctcatgaaag cgcttccaga 540

gctcggctcc ctgcagatcc acccgcgggg cctgcggcga gggcagaggg gtcccgggcc 600

gggccaggga gncgcgccgg agaccccttg ggggaagcct cccggtgacg ccagagggga 660

agctccytgc tggaagccgt cctcacagcc gcctggacag caaaggacag agaanaggra 720

actggtgagg gaaaacagag gggaagcmag ccgcggagac ggscccacct ggtggctgag 780

aagargaaaa tgaccgggag aaaaggggaa gctttggtgc catcaggtcc tcctaaagaa 840

caagccagtc gatagacacc cacattctgc ctgtcgaagg ggcgcattca gagctccagt 900

gtggcctgct tggtccccaa gtcccaagcc cggrakaggc gygcggsmag cgtccacmcc 960

accccgctgk gcctccgcag gkcsarggcm cmasmaraaa aggcttcacg ccgnccgccg 1020

gggtctggga cgcttgcccg acggagtcag agragctccc sggtcmagag tccacagtgc 1080

aaactycgac gcaacctgcg ccttgaarcg caagcagcaa aagcgcccsg cactctgktc 1140

ccaagagcyt gggcctcctt aagccataag cgtytgcggc gcctcgcttt kggccttctt 1200

ttgggccggg ccggaggmat cttctagaar gctcttyaga acmccgcttt ygycaaactm 1260

ycggncgccc tgcgcttcca rcccarcaga agaaaagtgt gaaaagcaag cccgcggtcg 1320

ccgtcggcct tggcagagaa atcaagagga gaagggaagg gaaccgctca actacccttc 1380

gggaaaccaa gtttccaaat atgccgccct cttcctggtt tgcacaaacg gtttagggca 1440

ttcgttccgg tttcagggtg gggtatgccg tcgctcccct cctccccgcc ctgtgctttt 1500

aaaagttagg aaacaaaaaa gagcacccat tggctggaac cccaagggag gcagatgcag 1560

gaagcacaga gctgcaccgc taggcgcagc aaacagccgc ggccgaaggc gcgggtcgcc 1620

gagtgggcgg cggccgc 1637

<210> 47
<211> 900
<212> DNA
<213> Homo sapiens 3.D.40

<220>
<221> n
<222> (1)..(900)
<223> a or g or c or t

<400> 47
gcggccgcgg cccggaccag ccgctcccac ccgccccagc tactacggcg cggcgcgacc 60

gcgggctccg gccccagccc aggcacgtgc gcccaggccg cggggaggcg ccggcgcctc 120

ccggaacgcg ctcctggcct gcgagtgctg cccgctcagt ctccgggtgg gaagtgcgct 180

cgccccggac cgaggggaaa gcccaacatc cccgggatgg aacagagagg cggccacccg 240

tgagtgggcg tgacccattg gttcccttgc gcagcatctg tggagaatta ggctttcccc 300

tcctctcttg ccagccgttg ttcctaatct tgtctttttt aagggaggaa agcaggagaa 360

ctcatgacac tttgtatcac aggaaatcaa gttggtggag agagggtttg ctgacctctc 420

ccgtcccttc tcagggtccc taggagaatt tttgaagaag taatcggcag caaggagatg 480

ggggcaatag agagtctcag actcgcaggg acccatgttc gtccccagcg ccactacttt 540

caaaccgtta tccctcagag ctgtttcctc acctccacaa caactctccc gggttcgatg 600

acactatata tcccaccagt tcatcttggt acaggccaaa aggtaattca aaaagcgaaa 660

cgaatctcat nttctgacct gtgccctcgg taaagtcccc angtttccac cccaagtaca 720

cttggaagcc aggcccctnc acacangctg ancaccacct tncacaaact gaaaacaaag 780

anaatccctt ggtttcaaag ttagaatagg gatacngcgt gagtggggtg aattgcnatt 840

gggtcaagga aaaaaaaaaa gtaaatnaat taantttttnt tgacctcctg cgctgcccac 900

<210> 48
<211> 1511
<212> DNA
<213> Homo sapiens 3.D.44

<400> 48
cgggcgcggc gagccccact ttctcccggc aggaaggggg gaggccgaga gcatttcctg 60

ttgtgcagct gagccctgcg gagacgtcat tgcattcatg ctccctcggg tgtcagcgga 120

cgggggggcca aagttcaagc cgcgtccagg gcaggcagcg cgcggcggcg cggcggcgcg 180

gggcgggcgg ccagggctcc cctctcccgc tggcgctccc ggcgcctccg tccccggccg 240

gcccagcgct gctaccggag gccagccctg gggctccgcg gggaagagct gctcttcctc 300

ccggaggaaa ccgagctcgc aagcccagcg ctcccagccg cagactgcag agctccagta 360

aggtgaaagt aggcaagaag gccccctgag acgtttctaa aagcatattc tatatgtttt 420

cattatgaaa acacccactg cactcctttt atttattagg accttaagtt atcctatctc 480

aactaatact tttaacaatc agaatctctt aagaatcttt caatcttata cttatccact 540

ttaatagcca acaaaacctt tagccagagt gttttaaaat ggaaattacc tgttcatgtt 600

tcttaaagat ttttaaagtc tccttctaaa tttccagcct tccatttagt ttcaagccat 660

aaaccagatt ataacaatgt gtaattgtag agaagctgtg gcttacggtt aataacgatt 720

aaaaataagg ccataaggta ttttatgatc attttgaaat aaaaaattga aatagtttaa 780

tttcagcttg tgcagtttga gacagatcgt caactacaaa acaaattgta gattctgttc 840

tcatggtgaa caaacattac agatgtttta ctgtgtcaac atctctaaca tttgaactaa 900

gcaatgtttc acatcagaac atgaattaaa acaatgtaaa ctatggacct ggggtgacca 960

tgatgtgtcg atgtaggttc ttggattata acaaatgtac cactctagcg caagacttcg 1020

atagtggagg aggctgtgtg tatgtgggga caggaagtac atgggaaatc tctgtacctt 1080

ccgctggatt ttgctgagaa gctaaaacta ccctaaaaat ataaactcta tttttaaaca 1140

tatgtttagg gttttatgag tatcctgata cttaaaatgt gcattgcatt gtaacctatg 1200

aattgacaag aaattaatct taagaattgg cacagaaatc atctcgatgt tttcatgaag 1260

ttcatcctcg gttctactgc ttcttgataa acaagtttca tgtttagaag gttactgaaa 1320

ttttttttata tggtaaaggc acatcaaaga ctttaccatt taatatatat tagttgtcct 1380

atccagtcat gtactattta aggcaatatt aaaggtaact tagatttccc cacttacagt 1440

gatgcaaagc ccttcaataa tattctgttg tcttatttcc taaacatctg aataatacaa 1500

ctttatcaca t 1511

<210> 49
<211> 835
<212> DNA
<213> Homo sapiens 3.D.60

<220>
<221> n
<222> (1)..(835)
<223> a or g or c or t

<400> 49
gcggccgccg cggagccggc gtccgcagcg gctgcgcatc tcgggcctgc agcggggcgc 60

ttggcgggcg ggggccgggg gagagcctgt ttgcgcagta cccccggagg gcggaaggcc 120

gccgaggtaa gagccgggac tcggccaggt gggagtgggc accttgggcc gggcctgcag 180

ggcggtcccc gagcgtcccg gggtagggtg ggctccctgg ggacgatgcc cagggccccg 240

gccgcgctcc ggtcgcgccc caccccggct gcagcgcggc cttggggcgc tgctggcctc 300

gccgcggggg tgggagcggt cgcggcctgg agcagctccg ggcgggcccc aggctctggg 360

gccagggcca gctgcgcgca ggggtgagtg agcagccccc gggccctcaa gtgagccccc 420

gtccgctccc caccttgcat ttctcctctc cgcagtgggc gtggcgcccc tttgctgtat 480

agggggcgcc ccaaattgaa gaaggctggg ggggagaacg cataaacagg tgtttagggg 540

gcccaggcct gtgcgccaag ggttgaagaa taaagagtaa ttctttttttc ccccttttta 600

agggggnccg gagtcccccc ccccccggc cgtggtaagg gccccccctt gctccgtaag 660

gggccctcct ttggnaaaac aactcctttt ttctttttt attttgtccc cccccnccca 720

ataatttaaa nncctccctg ntcgcccccg ccccccgctt ttttttttt tttttctnaa 780

acccccccacc ccccccccc cccttnnttt gtttccgctt ttattccaag aaaat 835

<210> 50
<211> 645
<212> DNA
<213> Homo sapiens 3.E.04

<400> 50
gcggccgccg gcttgacgtg tacggcgctg atcacctacg cttgctgggg gcagctgccg 60

ccgctgccct gggcgtcgcc aaccccgtcg cgaccggtgg gcgtgctgct gtggtgggag 120

cccttcgggg ggcgcgatag cgccccgagg ccgccccctg actgccggct gcgcttcaac 180

atcagcggct gccgcctgct caccgaccgc gcgtcctacg gagaggctca ggccgtgctt 240

ttccaccacc gcgacctcgt gaaggggccc cccgactggc ccccgccctg gggcatccag 300

gcgcacactg ccgaggaggt ggatctgcgc gtgttggact acgaggaggc agcggcggcg 360

gcagaagccc tggcgacctc cagccccagg cccccgggcc agcgctgggt ttggatgaac 420

ttcgagtcgc cctcgcactc cccggggctg cgaagcctgc aagtaacctc ttcaactgga 480

cgctctccta ccgggcggac tcggacgtct ttgtgcctta tggctacctc taccccagaa 540

gccacccccgg cgacccgcct cagcctggcc ccgcactgtc caggaaacaa gggctggtgg 600

catgggtggt gagccacttg ggacgagcgc caggcccggg tccgt 645

<210> 51
<211> 1021
<212> DNA
<213> Homo sapiens 3.E.50

<220>
<221> n
<222> (1)..(1021)
<223> a or g or c or t

<400> 51
gcggccgcgg gacggggaga tgcggccccg gtattgatgt cgaaaatgat ggataacgcg 60

ggaatggcaa atatactatt tgtctaatgg ctcggcaatt aaattcccct gtaaatgacc 120

catgcctcat ttcatcctaa tctatggaat tttgattgaa ttcgtcagct ctaattgaaa 180

aatactgcac tttaatgtct gcattgcagt ttcaggacga gagtggtttt aatgagacag 240

tgcccccatg acccgggaat atttgagact tttattcgga atttaaagcc aggagattgc 300

tcgactgagc cctgagattt cctctcctgt atccacgtcc atccatctcc agacgcgatt 360

taataaacgc acttaaggat aaatgcgccc ccgaccctcg cgccaacgtg ttaccccacg 420

ggcgcccctc ctcggaataa gggacggcgg aggccgggga ggcgggggag ttgggggct 480

cagaaggtcc tggtccctcc ccggcccaag tttccctgcc ctccctgcca ccctggtccc 540

caggcactgt cgcggacccc agactccgcc ttccctaggc caaacctagg cgacctccct 600

ggactaggag gcctggctgc ctgccacccg cgcaccggaa gaagggactc gcgcactcgg 660

agaaggggcc gggccccgac gcgctttata tgcaaatggc gaggcgaagc catccctgag 720

aaatagctac ttgctgaagc tatntactag attgaaatga gttaagagaa acatttaagt 780

cgtgcaacga gataattggg ccgattaact ggggatgttt gctctttcaa aaaaaaaaaa 840

aaaaaaaccg ccgaggagga gagagcagta agccgcgttg attgagccca ctgtcaagac 900

cgaattccga tgcgggacgg tcctcgggac tcgaagagac ccacggagga ctgagaggct 960

ttcgccggcc gcgcatttct tttcaggcat ccaccggcca gggcctagaa gtccgaaagg 1020

c 1021

<210> 52
<211> 518
<212> DNA
<213> Homo sapiens 3.E.55

<400> 52
gcggccgcag gaaccacgat gagaggcagg agctgctcct ggctgagggg cttcaaccac 60

tcgccgagga ggagcagagg gcctaggagg accccgggcg tggaccaccc gccctggcag 120

ttgaatgggg cggcaattgc ggggcccacc ttagaccgaa ggggaaaacc cgctctctca 180

ggcgcatgtg ccagttgggg ccccgcgggt agatgccggc aggccttccg gaagaaaaag 240

agccattggt ttttgtagta ttggggccct cttttagtga tactggattg gcgttgtttg 300

tggctgttgc gcacatccct gccctcctac agcactccac cttgggacct gtttagagaa 360

gccggctctt caaagacaat ggaaactgta ccatacacat tggaaggctc cctaacacac 420

acagcgggga agctgggccg agtaccttaa tctgccataa agccattctt actcgggcga 480

ccccctttaag tttagaaata attgaaagga aatgtttg 518

<210> 53
<211> 498
<212> DNA
<213> Homo sapiens 3.E.57

<400> 53
gcggccgccc ccacggctcc accctctcgg cggggccgca gccatctggg gcccctgcca 60

gtagcggccg ccttccgctc agcctctggt cccaggcgag cctggcgagc cggcgaagca 120

ccggcgggga ggaggactag aacaggagga ggggcacggc ggattgaagc gagctgggct 180

gtgagcaagg gacacccaca gcctggagaa acagccccgc tctcttgcgc gctgtctgct 240

ccagccgcta ctgggggctc taagcagcgc gatgctgctt cgcttcttct aggcggcggc 300

cggcggaggc tttccgcagc cgcttggccg gcgccggccc ctattccgtt ggcaagtccc 360

ttgtctatcc cggagggcgc acccggacgc tcgagccgga gcgagcgcga agtccgaagt 420

ccgcccccag agccgccaac ttccctgtga gcccctctcc ccgccgcagc ctgcgccaga 480

cctgggagcg atgcgccc 498

<210> 54
<211> 471
<212> DNA
<213> Homo sapiens 3.E.59

<400> 54
gcggccgccc gggcccgcgg gcgggggggat cggcgggggg gacccgcggg gtgaccggcg 60

gcaggagccg ccaccatgga gttccgccag gaggagtttc ggaagctagc gggtcgtgct 120

ctcgggaagc tgcaccggtg agcctggcgg gggtcccggg agaagagtgg gaggatctga 180

ggaggatgct aattcccacc tgggcgcaga ctgacagatg aacgggcgat accccggcat 240

gggggtccac ccatctgtcc agttttctgc cgtgggctcc gacggcgctg ttctccctgg 300

tcgagccttg tccattatcc tgttcctttt tctgcacccc accccacccg gctccactct 360

ctctggtgct gtaaatgcct ctctcccggg tctctggctc ctcccccacc acttctgggt 420

ctctgtcccc gtctctttct ggatgtctct gccccttttc tctctgggtc t 471

<210> 55
<211> 971
<212> DNA
<213> Homo sapiens 3.F.16

<220>
<221> n
<222> (1)..(971)
<223> a or g or c or t

<400> 55
gcggccgccg tgggcctgca aaacttccaa agtagcagcc tgtttctcct cgtctccctt 60

ctcctgggta cccagcgccc cgccttcccc agaaagggcg aggggtgggg gcagggctcc 120

ctcgggaggt ggccaagcgc cgggacgcgc tcccagcgtt actcaggaca cttgggattt 180

ggcctgcagc ccccttcccc atccctggcc tggctgcggt gtcccttgct cccctctgct 240

gctgctcctg ccccatcaag tcgaaaatct gagggtggga tggggtgggg gaccaggggg 300

taccctccca ggccgctccg cagcaggccg aggtggagac cctgcccggt aggcgagtcc 360

ttgtgcccac agctcggagc cagcagcgga gtgacaaaaa agataaagtt ggtgaatgat 420

aaagaccgta ttttccacgc tttgggtgcg ggaccagatg atctagaaaa tgagctgaaa 480

tggattcagc ctccgagcct gttgtgagag cagctgattc ccccatttcg ggccagatgg 540

ctgctgaaca cagatttgca ttcattttcg cttaatatcg tccaaaatag tggggcagct 600

gcatttgttg tcaaaaaggt ttaaaacccc ttttctttct ggggcaggat cgttacctta 660

tgtgatgggc ttatagaact ttttttttcct ctttagtcaa cagtatcaga tttagaagga 720

tttgttttta aaccttctaa tttggtaatc agatttaaat cgccttggcg cgtgtaatct 780

gaattaaaga tactgtaaat gattntaagc atgatacttt cgttagcgca aggaaggggc 840

acctctagca caggctggac attttaggaa gtgtgctata aaggagcatt gttcctattt 900

caacttaatc ttccgaaaag gctttggtat tctgcataac gctgctggcg ttgcctggtg 960

agcccgagag t 971

<210> 56
<211> 550
<212> DNA
<213> Homo sapiens 3.F.2

<400> 56
gcggccgcac gcgggtgcta atttgcacac atcaagactg aagtgtagtg aggaaacgtt 60

gagtttctgt tttcaaacct ttaacttcgt aattagagat ttaacaactt gaaggggggc 120

ggggagaggc gggggaggag gtgggcagaa ggaataaaac tccatctaaa attcctaata 180

gcaattcctt agaattataa actgcgagat gatcagaagt gacatctttg ccttctttga 240

aggctctctt ctctaagtta ctaataatga taatgcacgt tcgggtacag aaatatgagc 300

caagaactca agtctgcaat gaaggagtgg acatgacagc gtaagaggga gcatcattgt 360

ttgatctatt ttaacctttt ccgtctcaaa gatacgatgg tgcttcctcc aggaagaaaa 420

gcctgtaagc tcaaacaaga gctcccctgg aacagaagac actggagacc gtaagaggtg 480

ggaggttgga agggggaaaa ggatagaaaa actgcctgtt gggtattatg ctcaccacat 540

gggtgacggg 550

<210> 57
<211> 870
<212> DNA
<213> Homo sapiens 3.F.50

<220>
<221> n
<222> (1)..(870)
<223> a or g or c or t

<400> 57
ttagactctc actgggcagg tctgctgtcc cctctgctcc cgcaggactg gagccaccga 60

gctcgcgcct tcttctcggg gtgcgatttc tctcctcttt tggactcaag atcaatgctt 120

cccggccggc gcagatcaca cagcaggacc ccaggggaga ctgtggcctt cttcccgcct 180

cccaattccc caagaccgcc tctagaggct gctgtgtccg gagaactccg agcattttct 240

ggacacagat tgcctaacag aggaacaggg gttaggtggg gagcggctgg ccggcccaaa 300

cacagcagcc ccaagctggc tcccaagcct gggctctcca cccccgctcc catcctctct 360

tgagcacagt taggcccaac acccctgtcc cccaaaacac ctcctaccct ccctcccccc 420

cagcccccat cttcaggaac atcacagggc tcacactcac taaccgcgga gagcacatgc 480

aggccggagc cctcagcccg gcagctctcg gaccctgccc agctcgacgc ggactcatgc 540

agaagaggac attccgcagg taggtacaat cccagcgctg gggcctgggg cgtccggggg 600

gcggcctttg agcttccccg ataccgctcg cctgctcccg gagctgttcg gccgacggct 660

gcccggntcg tgcactttca gtanggcccc gctgactcta ctgcccttgg gctaggccta 720

ccggngatgc ccagactcct tgggacgctg gacccgcngc gcgggcggac acgcanngac 780

tccgctctnc gcccggaatc gttgagacgg aatctcagcg gatcccgcgt cgccgagcgc 840

cgggncaggg agaaaggccg tgtggcgctn 870

<210> 58
<211> 848
<212> DNA
<213> Homo sapiens 3.F.72

<400> 58
gcggccgccg cgtcgccgac gcccggcagg actgagcgca cggagcggcg gaactcctcg 60

ttcctccacg tgtagagcag cggattgagc gcggacaggg cgcagcacag gagccagctg 120

gccgcctgca ctccccaggg caccggcagc gagaagccgc tggccaggct cacccacacc 180

agtggctgcg tggccagcag gaagacgcag cagagcagca gcaccgacag gccgctgaga 240

cgccgctgtg cccgccgcgg gtgcagcgcg ggcggcaggg gctgggcctg cgccgggtgc 300

gcggcgccac cggggcccgg cgcgtgctgg gcgcccggga aggcggcggc ggcggcggcg 360

caaccgggca actggtgcaa catgtggaag ttgatcacgc tgacccactt gacacttaca 420

cacacgcagc gcacgatgcc caaatagcat tgcaacaaca tatctgtctg ctccaacaac 480

accacagaag ccatcaacac cagataatgg attctcagtg gcacagcacc cagccccagt 540

gcccaaagcg agaacaacat cactaggccc aaggccagct cccaaaacca caccaacatc 600

ccccccctagt gcacctttta tacaacaccc tgtaaataga caaccccccа ataataacca 660

attaccattt aaagcccccc aacaatttga aaaagaagga caaccgtaat tcccaacccc 720

acacaccacc ccctaaaaaa aaaataattt tcgccaatac cgtcccaatt tttaaaaaat 780

ttcccaaaaa cctctaatcc aaaaacccca accccgcctt cttctatatt tcaaaaaata 840

cccaaact 848

<210> 59
<211> 2770
<212> DNA
<213> Homo sapiens 3.F.82

<220>
<221> n
<222> (1)..(2770)
<223> a or g or c or t

<400> 59
atccanatat tttnnaacct ctaacaatga agagtannac acanactcaa ttttanaagg 60

cacaggacct atgaanacat tttatggtaa aagaaataca aatggccatt tcccacgtna 120

agatgcatct aacctcaatg gtggtcacag naaaataaat tacaaaaaan aaagttttgt 180

gtgaccatca gttaggnnaa ttaaatgctt cctactaatc ttttcatgat aagtannaac 240

atactagcca ggcatggtgg ctcatgcctg tattctcagc atgttgggaa gctgaggcag 300

aaggatacct taagctcagg agtttgaggc tacaatgagc tatgatcatg cactccagcc 360

tgggtaacag agagtgagac cctgtttcta aataaataaa taaatgagtg catgagtgaa 420

catacataca tacatataca cacacggttt tttacatgtt tatagagagt ataaatggcc 480

aatgaccttt taaggcacaa ttagcaaata tgtattgagt ggaaagatgc atgttcttgc 540

atgcaggatt ctacctcctg aaatgcatct gataacactg cttgaaaatg tgtgtagaaa 600

tgcccacact agcatgtttg tggtgggcat ataaataata gcaaaacaaa acaaaggaaa 660

aagaaaagta catatatgtg aggaaccctt ttggttatcc tgggtttttg agataatgtt 720

catagaagga aagcaaatca aatgaagagc aattgagcag gaaacggggg gaaataccct 780

cagagtaata agattatctc attacactta agttttgctg atgcttcaag tttcctgagt 840

aagttatgcg aagcatcttt ctctgaaaat cttcttgctg cagaacaaac catgtttagt 900

gtctgtatat gtctcaactt cctgtcccca cctggcggat gggaaaaagg acacggtcct 960

tgcttgtgtt ttggagtgaa agaagcatta aaggtcttgc agactttacc aaggattctc 1020

ctggtctcat ttcagatcca acttccaact ccaggcagcc tctgtgtttt tctttaatgt 1080

ataatcagga tgtacttcaa tttggactct attgctgttt ggcctgtata tgcagtttca 1140

agatagcccc atacacctgc ctgcaatgat ccttcaggaa tagaatgggc ttctgagttg 1200

aggaatttgg gagtatactg agccctttgt gtatttttat taagtttctc tattcatgcc 1260

aggagaaggc tgtggacaaa aagtaaagga ggagacactg gaattgtgat gtccaaagat 1320

tccaatgttc aaggattatt tgaacccttc acgcctcttt agccaccgcc gccgacagcg 1380

aagacgcgga gaaaaaagtt ctcgccacca aagtccttgg cactgtcaaa tgggtcaacg 1440

tcagaaatgg atatggattt ataaatcgaa atgacaccaa agaagatcta tttatacatc 1500

agactgccat caagaagaat aacccacaga aatatctgcg cagtgtagga gatggagaaa 1560

ctgtagagtt tgatgtggtt taaggagaga agggtgcaga agcagccagt gtgactggcc 1620

ggggtggagt tcctgtggag ggcagtcgtt acgcgctgat tggcgccgtt acagacgtgg 1680

ctactatgga aagcgccatg gccctccccg ggattacgct gggaggagga ggaagaaggg 1740

agcggcagca gtgaaggatt tgacccccct accactgata ggcagttctc tggggcccgg 1800

aatcggctgc gccgccccca gtatcgcccc cagtacaggc agcagcggtt cccgccttac 1860

cacgtgggac agacgtttga ccgtcgctca ccggtcttac cccatcccaa cagaatacag 1920

gctgttgaga ttggagagct gaaggatgga gtcccagaag gagcacaact tcagggacca 1980

tttcatcgaa atccaactta ccgcccaagg taccatagca ggggacctcc tcgcccacga 2040

cctgccccag cagttggaga ggctgaagat aaagaaaatc agcaagcctc cagtggtcca 2100

aaccagccgc ctgttcgccg tggataccgg cgtccctaca attaccggcg tcgcccacgt 2160

tctcctaacg ctccttcaca agatggcaaa gaggccacgg caggtgaagc accaactgag 2220

aaccctgctc catccaccga gcagagcagt gctgagtaac accaggctcc ccaggcacct 2280

tcaccatcgg cagggtgacc taaagaatta atgaccgttc agaaacaaag caaaaagcag 2340

gccacagcct taccaacacc aaagaaacat ccaagcaata aagtggaaga cgaaccaaga 2400

tttggacatt ggaatgtttg ctgttattct ttaagaaaca actacaaaaa gaaaatgtca 2460

acaaattttt ccagcaaact gagaacctgg gaattcctgc acagaagaca agagagcagc 2520

ctccccagtt tcagcaagcg ctaggtttat attttttcc tggtttttac tgtttgggta 2580

atagatattg aaacaagtaa tattaatacc gcatggggag aaccccaacc aaagaaatct 2640

gaaatataaa ataaatgctt ttttttccgt ttttgttcat tttggatgct ggcgctaagc 2700

ctccaagtgt catgattaaa aaaaaaatta tgtccttatt tatttctagg atgaggggag 2760

gataacattt 2770

<210> 60
<211> 563
<212> DNA
<213> Homo sapiens 3.G.46

<400> 60
gcggccgccg ccttccgcag taatggttgt tcagcgaaca agatccgggc ggaaacagta 60

gataggcggg tgcagcgggg cagaacatag gttgccttag agaggttccc cggtgtcccg 120

acggcggctc aagtcagagt tgctgggttt tgctcagatt ggtgtgggaa gagcctgcct 180

gtggggagcg gccactccat actgctgagg cctcaggact gctgctcagc ttgcccgtta 240

cctgaagagg cggcggagcc gggcccctga ccggtcacca tgtgggcctt ctcggaattg 300

cccatgccgc tgctgatcaa tttgatcgtc tcgctgctgg gatttgtggc cacagtcacc 360

ctcatcccgg ccttccgggg ccacttcatt gctgcgcgcc tctgtggtca ggacctcaac 420

aaaaccagcc gacagcagat gtgagcagcg gcacacgggt ccgggcaggg ggcaagggct 480

aaggaaggag tggctagggc aggggcggga accggggtgc ttgaccacac gtgaagactc 540

agaactaacc caggcagcct gga 563

<210> 61
<211> 4104
<212> DNA
<213> Homo sapiens 3.G.78

<400> 61
gatatctctc tccaagcccc cttcccaact ccatttctgt aggaaagtac agcccctgga 60

attgggttct ggtttcgctt tgggctggag gtgggtggat gggggtcaga gagagaatga 120

ggtgggggggg acttcaaggt tctgtcccac cgaccagagt ctgaagacta ttcgcctttc 180

ccaacacgga cctccgccca tccaggcccg ggactatccc ttcgcggtgt agcggcagcc 240

ggagacctgg ctgaggaggc aaccgcgtag acacctccct gcttagaaaa caaacactga 300

accagaccga tcccagttgg agggttcgaa aatgttccag acagcctgtc gggaggggtt 360

gttgttgctg ttggactaaa tagctattcc tgattggtca tgtatagggt tttttaaggc 420

gggtgggggg aggagggggt agaggaaagg ctccaaacac ctgcaggttg ggggcggaaa 480

gctgtttgcg attccctgga ctggttggtc ggggacagga ggtaattccc agccattgac 540

ccccatttct ctctctccct ccctcttgcc ctgcctcttt ctctccaccc ctatctttcc 600

tggaaactcg ctttgggcgc ggcagatcgc ccaggaccac accgcagcgt aactgcaggc 660

ctctcagcga aaaaggggga aagcaaagac ccgggtgtgc atcctcttcc tcggcttccg 720

ccccttttccg gcggagtgga gatcctattc agaggggccg gtctctctaa atatgcccca 780

ggtgagtttt caggggaatg gtgccggtgg aaacggtgtc taggaaggcc ttgtgttccg 840

gcctggggtg aggaaggctc aggacagagg agagcccatt ctcagattgg gggtgggggg 900

aggggaggac cagccagagc ttggaatcgg gatctgactg ctgtagctgc ctctgtggca 960

ttcagcggct ttttcccttt tccacccagg gtaaaaccag ctagttggac ttagtcgtcc 1020

aggcctttcc cattggtccc ggttctgtgg acgtttccca aggccggtaa ctttggggcg 1080

gctgtatccg ggtggtacag actgtgcctg gagctcccgc aggaggaagg cggcagcctt 1140

cctggctagt gcagtcccag ctcgagtggg ccctgatccc aggcctgagg cctagggtgg 1200

ggaggcagga acacccctct tctccggtag aggcgaggat ggtggtgctg ttccctggtg 1260

ggtttggtac ttgtgcaggc ttggggcttc tccagggtgt tgtgctggtg tgggcccaga 1320

agagagacca gaggctgggt ctaagggcct gaggctgttt tcatctaaga aattctctgt 1380

atgggggatt gggtctgctt gagacctgtc cccaggaaga atctcctggg gtcttctgtc 1440

ttgttctggc acaggtggaa atattctggc tgtctggcaa ctgcagatga ggatttcctg 1500

ttgggggcta taagcagggt ctccgtagta caaagagaga ggagctgtag tcgtcaaata 1560

ctctagaacg attcagtcta aaatctccct cctccttcat tctccccaaa taaaaacaaa 1620

caaaatctct cgggcgttcc tttctgtaat ccaaatcaag tgatgcagct tagtcgccaa 1680

caaccatcag tgtttgtgag tggcttcttt ggggcatgga cctctggctg gtaatcctaa 1740

accggcagga ttttcctaaa atgtggggag gagccgggag aggtcctcca cagatcctgg 1800

gatccaatca tatatttctt acaaggaacc ttggcgatgg gatatttata ggtgtctgga 1860

gaggacattt gtggccaggg tcaattcatc tggaatatgt actcccattg cctctcagga 1920

atccaccgct agagcaggag cctaagaatt aattggaggg taaaaatgtg tcataacaga 1980

gcttgagctc agtctgcaac tgcagtgcac actgtcactc ggttagaagc tggggcttaa 2040

gcatggatca ctgggctcac accggtgtgt caggacggag agcagtgagg tagggaacca 2100

ataccttgaa gcttgtatgt ttcccagggg ttggtatatt tctggcacat ttcgctgctg 2160

ctgggagcaa gaggacctgg ctgatatact tctggtgcat ttccagtggc cttggtgtct 2220

tggtggttgc attctatgga tagagaccta ttgtctccac caaaatcata aactcacttc 2280

caatgaagtg tcagggacct actgccttta cagcttgtat acaccaggac ttagggaatt 2340

ttgtggtttc tgtgccagac ctgggggggct ggcattccca aagaaggtgt acagcagtct 2400

gaatcttgac tctctgtcat cctgggtgtc tagtggcaat tgagccaagc tccagaggag 2460

gctgcagatg atccattctc ccttctgggg tgggagggat ggttcctagg atgactcctg 2520

tccagagcat tgcagtggca gtatgggagc tcaatggctg ctatgtatga tttagatgga 2580

ctctgcatgg gggtaaattg ttttttgta tttgttttct tcttttaaat acccaattat 2640

ataattcaga gagcagaaag cttattttaa acaacttatg tggtgttgat catatatgta 2700

caactcacaa ctcacaaact ctggcccttg agtctcctga tttttctgtt ttggttcttg 2760

ctggtgccca gctctatctg gatgaagcca ggtgatggaa gagccccagc acacctgtgg 2820

gaagtagagt ggctgtggtc atctcggagt atgcttgtgg ggtcacaagg tggtttcact 2880

gctctgggaa tacaggaggg ttgagcaaag tgagattatt gctctggtct ggctctctca 2940

cagataggct gtgagtgact tgacattcgg ccaggcagtt ttctcactgg cccattctcc 3000

ttgttaataa tgtttacttg aacgtttgca cagcactttc aaatgcataa aggaggtatt 3060

cctcccattt cccaaagaac accaaggcag gagatggcgg tgaggggggc tggaagagtt 3120

caagggcctc atgacatcct gtcctgctct tggatgggag tccagacccc actggcctca 3180

gggaaccctt caaatgccca gctccattct acctcagcca ggcctctctt tgagactcga 3240

cctcacttca gagtccagct gagcagaacg aggtggactg tgcagggagg ttgggccagc 3300

accatcttct tcccttggcg acctctcatc tctgtctgag tgggagtaaa gatccgctgg 3360

gcgggcagag gactcacagt ggatttgctc agtgtagaca gacactccct cactccccag 3420

cgggggcgaa tgtgtgtgtg tgtgtgtgtg gagggagctg gttcctcggg attattctct 3480

gccagctctg gcggagtgga tcccagtccc cgtagcctcc actttctaat tccctacttc 3540

catccgcacc gggtttctgg gtgtgtgcct gtaggtgggc tgggaatatt gctgagaggc 3600

caagggaggt tcctaaagca acgaacccct gcctgacaga ttccccgcta aaaccaaaga 3660

gcacgatccg gaatttgttc cctcctcttc cctttaggcc tgagaaaggg gacagagtaa 3720

tctctttctt gcctccttgt acatttcctt cctcctgatt tccccttctg tgtttctgtc 3780

gctggctgta ttccttttct tccggtgtct ctgtcgtctt cctccatctc tgtccttttg 3840

gccctcagtc tctgtgtctc ccaggcaccc ctcccttctc ccaatccaga gaccctcttt 3900

ccctcccacc ctagccccaa ccggcctccc gccctagccc cacgtggcgc taactttgtc 3960

tgcctcttct cacgtctcgg tgcgtgagtt cctctctctg cccttctccc ctttacccca 4020

gcccacgtcg gtgggtcagg ggcggtcgtc agagcgggca tccgcttgtc tgtctgtctg 4080

cccacaggat gaccgagcgg ccgc 4104

<210> 62
<211> 570
<212> DNA
<213> Homo sapiens 4.B.44

<400> 62
gcggccgcct gtctgggcgc cgcgctcctg ctcctatgcg ccgcgccccg ctccctgcgc 60

ccgggtgagt gcccgccggc cgagccgcgc acccccaacc aaacctggct cctcgcgctt 120

tccaccgcgg cctgacccct cgacagcgcg ggggacacct gttgtctcct tcctggctgg 180

ggctaggggt ggcgggcagg ggcgctggtg cggcacagaa aggctctaga cgcccccgcg 240

agcaaaggct cttgctcctc ctccggagtt acctccccac tcccagagcg gtgactgttt 300

tgagtcccac agccggtgcc tggagaccgg ggtcagttgt ggggggtaga ggacaattgg 360

ccaatccggg aaggccatct cccttacctt caccccccttc ccctgcgcac cccacggccc 420

ctggacatga gcgctgctgg gcgcatgcgc ataggagggg aagcttgggc cactcggtcc 480

ggtcccttgg ttgtcctact gtgcagtggg tgccactccc tgctccaccc tgaaatccac 540

actgggtagg gcttgggact cctgtgcacc 570

<210> 63
<211> 535
<212> DNA
<213> Homo sapiens 4.B.56

<400> 63
gcggccgcgc tttctccatg gccccggcct cggcgcgctc ggctccggct cgggggtccg 60

gcacggcagt ctcagtgcgc ggtcgccagg cgcgccgtcc caccccggct cggcttgggg 120

gtggccccgc gcctccgccg ccgacgcagc tagctggttt ttaaattgct aatctcatta 180

acggcgcgcc cgtccgagag gcgaggctgg taaatggatg acggcgagcc ccaccccgcc 240

cgatcgtcgc ggccgggaag gcacccgaga ttgcagagga cagggcggag tcccctgggg 300

tcctccggct cggcggggcc tttcttcagg ctgcggaact cctcgaagtg ggcgccttcc 360

ctcggccact cacctgtcat ttatcgagcg cctactgtgt gccaggcatt gtctggggac 420

acggctgtga accacttccc agctccgtct tggagctgac attctggtag agggaaacac 480

ttgaattgga ctgcatgaaa tgccccattt tcaaccattt tttaatttat agaaa 535

<210> 64
<211> 737
<212> DNA
<213> Homo sapiens 4.C.05

<400> 64
gcggccgccc ggcggggtta aggcctctca gccaaggccg cggccagctc actgccaggt 60

cgggtcagcg cctgcgcgcc aggtccggcc ttggataccc tctgccgcca cgcgtcggtc 120

cggcctctac gcccgcctgg ccctctgcgc gcgccgccga cgccgcaggt ccgggcctcg 180

gtgactgccg gaggggcgcg gcgccccgcc tcctgtcacc atggccaccg caacccccttc 240

caccgcctca cggccggccg gcatccaatc acaggcgagc gttaccgatg ccggggcggg 300

gcaagacagg gagaggaagt cccggaaggg agtgcggagg gatgcggcgc ttcggcgagc 360

acccgttgtg tgggaactcc gtctcaagtc gcccccattg tacggatgaa ggaatcgaag 420

ccacgagcca gaatttcctc actcgcaact cgagaataaa ttgcgcctcc ctgagtgtgg 480

aggattaaat aagtagttta aggcgtgttt aaagagcgct tgtaagttgc caagtcgctg 540

gagagccagt cccttatccc ttgaaccagg tgatgctgac gtctgatttc aagacagttc 600

ctacccctcg tggaaggaaa gccccatcgc aagaagtcga tgtcctgtaa tttacgttat 660

aatcttcgca tcataaagat tactcggcag taattggttt cttgactaat tataccagat 720

gagaattgaa gactatt 737

<210> 65
<211> 684
<212> DNA
<213> Homo sapiens 4.C.25

<400> 65
gcggccgcca taggaaacac ctggcagtta gttcctcaaa aggttaagcc cagaactccc 60

gtaagaaccc gcaattccac tccttagtat agacccgaga gaaaacatgc gtccgtccac 120

gcaaaaatct gcacacgaat gttcacagaa gcatcaggca taacagtcga aatgtagaga 180

caacccaaat gtccatatgg atgaactaac tgtggtccat ccatgaccgt aatggaacac 240

gaccataacc aggtgtgaag ttcagctgtg acagggatga ccctcgaaca cggcacgctt 300

ggtaaaacaa gcccgatgca gaacagcacg attctattta tgcgcctgcc cacaagaggc 360

acaccccggg aaagaaagca gatcagcact tcccaggaac cgggacgcag ggacgcaggg 420

agggagggac tgctgaagat gcacggcgtt tcttttggga tgaagaacag gttctaaaat 480

cgactgtggt gatggctgcg taaatcagtg aatacactaa aaaccttact gaactgtata 540

ttatttattt atttattgaa acagagtctc gctttctcgc ccaggctgga gggcaatcgc 600

accatctcgg ctcactgcaa ccttcgcctc ccgggttcaa gggattctcc tgcctctgcc 660

tcccgagtag ctgggactac aagc 684

<210> 66
<211> 1012
<212> DNA
<213> Homo sapiens 4.C.42

<220>
<221> n
<222> (1)..(1012)
<223> a or g or c or t

<400> 66
gcggccgcgg cggcagcggc tgcggggagc tccagcagcg gcggcggcgg cggcggcggc 60

agcggcagcg gcagcagcag cagcgacacg tccagcaccg gcgaggagga aaggatgcgg 120

cgcctcttcc agacgtgcga cggcgacggg gacggataca tcagcaggta cgcggggagg 180

tacgaggaaa ccgacaggag cgagatcagt ccctccgcgc gcccttgacc cctgctctgc 240

cccctcgccc caacttgcgg caagttgctc agaagctcgc gggaaaagtt ggccgcgact 300

ccgagagcgc gtagccggct cggccacgaa ggccgagggg actgctctgt tcgccttgcg 360

ggggtgccag ttggtccaac ttttcccagc gctgtctttg tctaggcgtt gggagacatc 420

tccttaggat gcgcactctt ccgggggctc ggagtgttct tccctgtggg aaaaggagtt 480

ctggccgctt gtcccaggta ggaggggctg ccccacagcc tcggggtcct gggcatcaag 540

atgccgcagc acggggcagc gatctgcccg gcggcttggt ggacacccca gggccgcacc 600

gggaggagat gagctaagcg acagcctcgg acagggaaat aacctgtgaa gaaactttct 660

tgtgccgcag aacccatgaa ttccaaactt cagagcccaa gaatgggtat cgtttgccac 720

ccagtattga tttaaacgca gtagcctgag aggaacgaag cgctcaggag caaactaggg 780

ctagacccga ctnctacccg gctctgtgcg ctgaccaggt gagcttcggc gtggttccgg 840

gcgcctcgng cctcactaca acaacttttg ggtgttgctt cgatccccga cttctacaga 900

gcngattaag cttctgctcc ngctgncaat atactctgcc aattggacta acttgngtga 960

gaagatccac ttctgatgct ttgatgtgca cgctgaatgg ttccngatga tg 1012

<210> 67
<211> 595
<212> DNA
<213> Homo sapiens 4.C.9

<400> 67
gcggccgcct tgaaggcgct ggacgggatg gtgctgaagt cggtgaagga gccccggcag 60

gtgagctcgc ggcccgccag cccgctgccc acgcagtagt ggaagaggcc gaagtagcca 120

ggcttggggg tgctcacgct gtcgcccacc cagtagggct ggatgaagac caccacgttg 180

atgatggcga agcagatggt gaagatggcc cacagcacgc cgatggcccg cgagttccgc 240

atgtagtgct cgtggtagag cttggaggcc tcctgcgagg gcagcatggt gcccggaggc 300

ggggccggcg gcggcggcgg ctggcggggg ccgccggccc gggacggagc gccgggctgc 360

cgggcgggag ctggggacgc acgcgagaag cggccctgag tcaaggaacc cgcgagggcg 420

gggcctgggg cagagctggg ggcgtctggg agctgctaag ggagagagga aggggtcatg 480

agagtgttga ggccgtgtct agggggactg gcaaaggtct cctactgggg ggcctaggaa 540

ggggccatga gaaagttggg gggcgcctag gatggggata tgagacctga agtgc 595

<210> 68
<211> 1955
<212> DNA
<213> Homo sapiens 4.D.07

<220>
<221> n
<222> (1)..(1955)
<223> a or g or c or t

<400> 68
atatctatcc atatctatac ctacatctac ctgtatgtgt gtagtgtata tatatacata 60

ttatatgtgt gtatatatgt acatatatac atttaaacaa aaatttctcc ttcgtcctcg 120

aagcaaacaa accagcaccc tcgagtgtcc gccaggaggc gcaggggca gcgtgggacc 180

tgcggtacct ccacggttgt agaggtgtag agggatgccg cagcgacgga accgggcttc 240

ttttttaaag aatcaatgtg agggaagggt gcagagccgc gttatttcag ggagacattg 300

tcgcactccc cctcccacgt gtaggtagca tctggggtgc gtgcgccctg ttcgcagacc 360

ccatggagag acgctggcgg cggcagatgg ggctcctttc acggttgcag ccggcagtaa 420

cccgaccccg ccggcgcaga gactgaagaa gcgcakggga cagcggcgag ctgcgaacaa 480

aagcccttgg cgcggggccg aagcccakga cgcggtgtga gtaaaccggc tcgggtaccg 540

ggagctgcgg gaacctgggc ggccaggttc tttgcactcc aggagcccac ccactgggat 600

gctgtggggg aactntcgga gggcacccga rggcgggtat ctgaaccccg actggggtgg 660

atggtatctt tagcacattc agacttggag gagawycggk gcggtctgag artatccagg 720

caccttctcc atccccagca aaacamccgg tgggggtggw ggtgggggcg gaggcggcgt 780

gcagagccct cagtaagccc tgccagagct gctggagcaa gaatccatca cccctcccgg 840

agaggccttt ggggacttct cccagccctt taatcacccg ggggccttgc gaccgagtct 900

cctttggcag gggaaatcaa ccataaactt cttyccytag gcaaatgggg tcccttggga 960

tgaacaggcc tcttgctttt ttgttcctgc aaagctgcat ccccagtagc ccgcctaagc 1020

tacaaacaaa tacgctaatc ctcccgggaa tcctccagcg cctccctctc tagctcctgc 1080

ctgcacctgg atcttttcat cttaacttgc agcagaaagg ggatgcatct agcgggctag 1140

gcgcccagag gagcctcgcc acaggcctcc accccgcatt ccgggggctg agggagaccc 1200

aggctgctct ctgaacacga gtgtccgccc caccccmatc ccsgtyytgg cgctcagcct 1260

gggctttccg acatcggttt tatgatttac gtyccaccaa agcctctgag cctaatccga 1320

aagcggatta agttgggatg gggtgactat ggatgaggag gggggaagag ctctcagacg 1380

tattcctcga tgtccctcct tgtgatctgc agagattcca acaaaggacg gggctcagcc 1440

atggtggacc cagtgcctga agaagagaag gcaggagcgg aacccggcga ctctggaggg 1500

gacgaggccg tggcgtccgt gccccctgat tcccagggcg cacaggagcc cgcagcctcc 1560

tcggcctcgg cctcggcctc cgcggcggtg ccccgcaagg cagaagtccc atgtgcagcc 1620

gcagaaggcg ggcggcggga gcagtccccg ctgctgcacc tcgacctctt caacttcgac 1680

tgcccagagg cggagggcag ccgctacgtg ctgaccagcc cccgctcgct agaggcctgc 1740

gcccgctgtg cggtcaagcc ggtggagctg ctgccacggg ccctggccga cctggtgcga 1800

gaggctccgg gccgctccat gcgggtggcc accggcctgt atgaggccta cgaggcggag 1860

cggcgcgcca agctgcagca atgccgggcc gagcgcgacc gcatcatgcg cgaggagaag 1920

cggcgtcttt tcacgccttt gagccccgcg gccgc 1955

<210> 69
<211> 1888
<212> DNA
<213> Homo sapiens 4.D.08

<400> 69
gcggccgcca gctcacaaag gatagggagg gatattgctc ttggcatttg atgggaagca 60

tctgctgcat cccattgggg tgttgcccag gatggattgg aaaagagttg gcaggaaggc 120

tgagctctgt gctcacaacc tggcttggtg gtggccgagg agcttggcag gagcagagtg 180

caggacctgg gaactggggg ttggtgcatg tgtgcacgca cgtgtgtgtg tgtgtgcgtg 240

cgtgctgggt gggtagggag gaagctgtga aaccacatcc cctcctctct gctgctgtgt 300

tgctgtgtgt ttcagcagca cgtgggtgtc accacacttc ctagcaggtg tcaacctcca 360

agactgttct gggctcttct cccagttggc tgagttggag gtgggagtcc caactgtccc 420

ctgtggcttc cagagtggga ccttgctgtg ggataggctg gccaatggtg ctccctcccc 480

tgtgaccctt ctgttgggtg ggtcacgagg aaggactgtg ggtgttgccc acagacaggt 540

ggacatgtgg caaggacacc ttgggacctt ctttctgacg ccccttgaag ggggcacttt 600

ctcagctttg agatgagtct ctgtggatgt gggaagttca ctatctcaag agcagcagcc 660

ttggaaaatc caacacagaa ccccgagtag gggcgggaag gggtcctgtc ccgctcactg 720

gctgcctggc agagttctgc acaaggaagc gcctgtgttg ctgtgggcgg aggaatggac 780

tgagggctac attcgcttcc tgttgccgct gtaactgctt atcacaaact cagtggctta 840

aagcaacaga ggctccttcc tttacagtgc taagggtcag aagccgatca gtctcaccgg 900

actaaagtca aggtgttggc agaatccatt cctgcctctt ccagctttgg gtgggaggct 960

ctgctggagt tccttggctt gcggctgcat ccctccagcc tctgcctcca tcctcctaca 1020

gcctcctcct tctctgcagt cagatctccc tctgccttcc tctttttttt ttttgagacg 1080

gagtcaccca ggctggagtg cagtggcaca atcttggctc actgcagcct ccgcctcctg 1140

ggttcaagcg attctcctgc ctcagcttcc cgagtagctg ggattacagg catgtgctac 1200

tacacctggc taatttttgt atttttagta gagacagggt tttgccatgt tggccaggct 1260

ggtcttgaac tcctgacctc aggtgatctg cctgcctcag cctcccaaag tgctgggatt 1320

gcagccatga gccatcacac ctggcctgcc tccctcttaa aggacgcttg tgatttgggg 1380

cccacctggg taatctcttc atctcaacat cttcagttac atctacagag tccctgttgc 1440

cacatgaggt aacacagttt gggaagggag agttattcag cctaccctag gggcctgtgg 1500

tgtatctcag ggcccttctg attttaagat ataaagcaag aaaacaaact ggctcaaggg 1560

gaaaaaagga cacgttgaat tctgttgctt taaatgtata ttttttttatt gtgctaaaat 1620

gcacagaaca taaaatttgc cattagtaac actgagtaca ttcacagtgt cgtgcaacca 1680

tcagcactgt ctagcgccag aacttttttca tcaccccaaa gggaaacccc gtatccatga 1740

aggactcact ccccattcgc cctctccagc ccttggcagc caccagaatg ctttctgtct 1800

ccataaattc atttttaata agtgcaattc tgtgtgactt taaaataaat aaacatgagc 1860

acgatgagtt gcttattgga aggatatc 1888

<210> 70
<211> 994
<212> DNA
<213> Homo sapiens 4.D.12

<220>
<221> n
<222> (1)..(994)
<223> a or g or c or t

<400> 70
gcggccgcta ggaaaaggct cagctccggc cgctccgatt agccgtggcc ttgctctgcg 60

agcagataaa cgtgacctcc gtggcctgtg gccagcctcg gccctctgga ggcggggctg 120

tgtgcggccc tcccctcccc agcagggctg agctcagaag cagcaggcag ccggaagggc 180

tgggcagtcc ccgcacctgt ccctgtgcca gtctggtggg tgttgtgtgt gcagggtggg 240

cgtgccggga ccctctggcg tggggctgtc tggcaaaggg cgaggggga gggggctgtg 300

cttcagcata gaagggaagg gcgtgtccag aagagggaac agaagagggt ccagaggccg 360

aaccagaaca cgtcccttca ctgatggaaa cttcccaccg cgctcgaatc aattcccaat 420

tgctcgactc ctcgcacctc ccgggaggtc ctgtagaggc agcgctccct cccagcctca 480

cccgccggcc tgttcctgcc acagggctct gcccttcctg agctctccgc ccggactctc 540

atcccggact ctcctcccca tctccttcca aagccagttc tttctcatta ctcagggctc 600

tgctccaatg ccacctcctc ggaggggcca cctcatcctc tgaacggcgc ccatccctcc 660

ctcctttctc ggngccagct ccattntccc cttctccttt ntcaccacgc ccacaactta 720

gaggcgcgtg tcccgtccct agaactgctg cggncacagg actnctggcc cttngcatag 780

gctggcacgt ggcacgttcg ccccagcctc gtacgcattt tgatggagag ttggaccaga 840

gagggcgcgg agcatgaatc tctgaagagc tgaggagccc aaatcagaag ctggtgagtg 900

agtttaatct gacttggagc atggagttat acgggagctg cttccagaag cccagctctg 960

cactgctacc atatatggca cggacgcttt agct 994

<210> 71
<211> 677
<212> DNA
<213> Homo sapiens 4.D.13

<220>
<221> n
<222> (1)..(677)
<223> a or g or c or t

<400> 71
gatatctttg ttgcattgag acaggaaagc tattttaaga tggtgtggtg aaaaaggata 60

aaagctcctt actcaagctc tagcttatct aactctcagt caataggtaa caaaacaccc 120

aagaagctgt taactgcaag ctcctatttc agagggctag ggacttcccc agatccccgc 180

ctgtacagtt agacttaaac tccaacctac atttaccccc tcctcacttt aatgctaaaa 240

attactcctg gggtggagat ttaaaatgct aatgctacat atgatgtatg aaaaagcata 300

ttgggccact gtgcaagcac tagaaaaact cctcctatag gtgccctgat gntaaccctc 360

ccctatagaa agaccctata aaactgaccc acacactatc ctcagagcag tccgttcctt 420

tgcctttctt ggtgctgact cccttgcgca caagctgaat acactttcct ttgctgctat 480

gtttggtgat ctctgttaat ctctatcatg ggagatcata agaatccagg gcaacagtaa 540

cagcttctga gtttttaaat taaaaataac agtaatataa tccttaaatt tttaaaatgt 600

aggacactaa acaagtaaaa tctaaatcca gagtacatct gacctcaaag ttcatgggct 660

tctcacttcc ctggcca 677

<210> 72
<211> 435
<212> DNA
<213> Homo sapiens 4.D.47

<220>
<221> n
<222> (1)..(435)
<223> a or g or c or t

<400> 72
gcggccgcgt nccctctcgc ccgnaaagag gactggagaa ggggctgggg tggaggtnnt 60

ctctgtgtgt gtctanggtt gngggcagga gaggttaatt ctattaagan ntcatcaatc 120

anccngtgtg cacttttcgc tcgacancgg ntcctnctac ttnanagcaa gtctggncca 180

gctgggatcc gaccagaaac cgcaagcgna ggagacgcat gancgnaggc tgagcgctaa 240

ctgaaggcnc gacctgagcc ctgcagcctg ctggggagct gcgcaaccac ggacagcagt 300

tcggcaatac acggcctggn ctgcatggcc cccgtcacca cctcacgtgg gaagccagca 360

ctgctgccgc cagccctgcc gctgccctca gactnncaag gcgnccaggg tcctcccaac 420

gcgcctgccc cacac 435

<210> 73
<211> 2343
<212> DNA
<213> Homo sapiens 4.E.53

<400> 73
tggccaggtg aggtcaggct ctgtttcttc cgagctacca tcctctacct gattcctcac 60

acctttttct tgttaggcgc agctaagaga cagagagaga gagagagaga gagagagaga 120

gagagaagcg actgaaacag agagtaaatt ctagtttctc ctttttagtc tcttttcttc 180

tgccctttgc tctgctagtt tatctgcgtc ttttctcttc tcgcgctgca agagtggaaa 240

actcgtgctc agttctaggc aaacattaac cccgggcgac gtttccaagc gggagacaaa 300

ctctagagag tgagaagcga gatgcgaggg caccaagggc aagaaggggg ctcggggtac 360

gccacgttgg cgggacgccg ccgccgcctc cctctgctgc gcggcctgcg ccgggagcct 420

ggtgggggcg gcaagacgac agaccccgcg cccgggcctc ccaccagtga ccacctccct 480

cgcagcttgg gctgatcctc cagacagcat gcaacggtgg ggagggaagt cccctgactg 540

ggcgggggac ctagcggctg ctctgaaact ccgaacacct gaagaggagg cgcggaaggt 600

ccagccgccc aagactcgca ctttcccctc ctccgcagcc cgggcaggtt accgtcctgg 660

gcctgggtga gcgcggaggg gatccgggcg ggagctgagc tcggttcccc aggcctgaca 720

agtggccgcg tggcacgacc aaccccgggc acagggctgg ggctgctccc caaggtgggg 780

aatttaattc tcacattttc gcactaccct gacggagctg gacgcgggaa gcgggaaaga 840

cccgttcctg tttgcagtgc ccgaggggca ggacacctac cagaagggct ctatcacagt 900

ggtgttaggc cgggcgcagt ggctcacacc tgtaatccca gcactttagg aggccgaggc 960

gggaggatcg cttgaaccca ggaggcagag gttgcagtga gccaagatcg ccccactgca 1020

ctccatcccg ggcgacagag ctgtcttgaa aaaacacaca aaaaacaaaa aacagtggtg 1080

ttagagggat gggattatag gtgacatgac tttcgttttg aactttcctt aaccttgcag 1140

gggcagccgt gccctgaaaa cgcctgtgat ttggagtaga gggtccaggc gcagtgtggt 1200

gagtgaccct aggcaggtca ctagttcttt ttcagccttc actgaatcct ctcttacacg 1260

gggatgttac ccccaggtct ccgtgtcttt cagggagaaa ttagttcatg agttagatgg 1320

tgcactatca atcatccttt tattagacag aaacaataag tttgaggaag aggacgtcta 1380

ccttacaggg ggtttaattt tcagcttctt tgagataaaa ttcattgaac ggtgttttac 1440

gtgcgcgcct tttccaacag accccacgcc tattcccagc gccagaggcg gacaaccgct 1500

ttactgagat acagagacag gtacttcctg aggcacttca gtccagttcc actgggttta 1560

ctacaactaa taatgactgt ttctgtttac taggtattag gcgatgtgtt ttaagtaaat 1620

gaattgtctc taatcctcac aactctaaag caagttaggc gtcacccgca ttttacaaat 1680

catagcgccc tgctcaccat atctggaatc ttgcctcgcc ccgagggttc taattttcac 1740

tttagagagc tgagcaagat gattgcccag cgctaactcc gtgaaatccc tgggactgaa 1800

aatcacaggt aactcgccag agtttttcaa ttttaggcct aggagattat gcaaagattt 1860

ccttcaagta aacgctgttc tctggggcct ctgggatcta cagtcggaga aggggaataa 1920

gtcccgggcc ggtgggggat gggtgggtgc agtttcctaa atagaggaaa gccactttca 1980

ttcaaagggc tgtggaactc tggctagagg tgggtttctt tgcagttaat catctgcaag 2040

gctctttgga tgcctgattc cagaaaccca gaactcacac ttagggtcac aaaatccagg 2100

gcatttattt gccgagcccc atggatgtta tccctatgga tgcaccccgc ccctgtccgt 2160

tctcctttgg agcagaacga aacccattcc agagcttttg caggaagtct tcaggccctt 2220

gcgtccggcc cctttagaca tcaaagcccc ccctgagagc aaaggacttt gaaagatagg 2280

aaaagctcag gatccttatc gcgtctctgc tccctcccga cctagtcgta aattccgagc 2340

ctc 2343

<210> 74
<211> 507
<212> DNA
<213> Homo sapiens 4.F.15

<400> 74
tacgactcac tatagggcga attggagctc cacgcggtgg cggccgcggg cagtgcggac 60

caggcggggg ccctgtggct gccggccaca tcccggagca acagcagaaa caacggcagc 120

agcagcagca gcagctgggg cccgggtccc gggctggtcc gagcggggac atgagccatg 180

gcgtggtgag ggcggcaaag ggtcgaagtc caggaggagg aaggcgagcg ctggcgcacc 240

ggaggctgcg gactgacctc gcggcagtag ggcgcgcggg gagagcccgg gcagcagggc 300

gctggatacc gaggtccgcg cggggcgagg ggcttagcgg agcaggcacc cgggcgcgcg 360

gtccgtgggt accggtggcc cgagcccccg gccagcggtc acagccgtcc ggagcagcgc 420

agagccgagc cgagcccgag tcggcgcgct gccttggcgg actcgcgctg cgaaagtttg 480

tagcccactg cgcgcccggc ccggctg 507

<210> 75
<211> 446

<212> DNA
<213> Homo sapiens 4.F.17

<400> 75
gcggccgcac acacgagggc ccgtcgcgcc ccccgccctg ccccgcctcg ccctccacgt 60

ccctgcaccc ccgagtcgca ctaagaaccc agtccccgat cggtttcctc tacgccgtct 120

gagcagaaga gagtgggaac cggggtgacg gataaggggg gggcgcccac gcgacgtcgg 180

ggtgcatggg agcgcgcggg aggcgctagt gggtgcacgg ggcgtgaggg ggacacagcg 240

cgggcgtggg gatggccact gcgcggggag ggttctgcct ggagaaggag ggatgggagg 300

aggttggggg agcagggcgc gtggaggagg gaggttggac gtgtgtacag cgcctgggga 360

cctcgctggc cccttggtgc ccccaggact ctgaggcttc tcctttcggc ttgaaatgtt 420

tttcccttcc tgcttttcaa atctgt 446

<210> 76
<211> 424
<212> DNA
<213> Homo sapiens 4.F.22

<400> 76
gcggccgcct tgaaggcgct ggacgggatg gtgctgaagt cggtgaagga gccccggcag 60

gtgagctcgc ggcccgccag cccgctgccc acgcagtagt ggaagaggcc gaagtagcca 120

ggcttggggg tgctcacgct gtcgcccacc cagtagggct ggatgaagac caccacgttg 180

atgatggcga agcagatggt gaagatggcc cacagcacgc cgatggcccg cgagttccgc 240

atgtagtgct cgtggtagag cttggaggcc tcctgcgagg gcagcatggt gcccggaggc 300

ggggccggcg gcggcggcgg ctggcggggg ccgccggccc gggacggagc gccgggctgc 360

cgggcgggag ctggggacgc acgcgagaag cggccctgag tcaaggaacc cgcgagggcg 420

gggc 424

<210> 77
<211> 558
<212> DNA
<213> Homo sapiens 4.F.6

<220>
<221> n
<222> (1)..(558)
<223> a or g or c or t

<400> 77
gcggccgcag ctcaccactg gcctagagat gccctttgcg aggcggcagc aactgacaag 60

atggtcgcgg gtcgccgcgt ccggagccgc ccaccaggtt gccaggagga ggcgggagcg 120

gggatcaagc ttatcgatac cgtcgacctc gagggggggc ccggtaccag cttttgttcc 180

ctttagtgag ggttaatttc gagcttggcg taatcatggt catagctgtt tcctgtgtga 240

aattgttatc cgctcacaat tccacacaac atacgagccg gaagcataaa gtgtaaagcc 300

tggggtgcct aatgagtgag ctaactcaca ttaattgcgt tgcgctcact gcccgctttc 360

cagtcgggaa acctgtcgtg ccagctgcat taatgaatcg gccaacgcgc ggngagaggc 420

ggtttgcgta ttgggcgctc ttccgcttcc tcgctcactg actcgctgcg ctcggtcgtt 480

cggctgcggc gagcggtatc agctcactca aaggcggtaa tacggttatc cacagaatca 540

ggggataacg caggaaag 558

<210> 78
<211> 865
<212> DNA
<213> Homo sapiens 4.F.69

<400> 78
gcggccgcag cgagttttct ggcagcgcta gcgccgcggg gcctgggttc ccgggttccg 60

gtctccgccg gctccgggct cgccccgcg agttggccgc accgttcccc cgcccgcggg 120

gcagccgctc ctccgggagg ctccggcagg gaccttcgcc ccggcccccg agcggcagtg 180

cggctccagc tggaggcctg gcccgggaag caaagtgaaa ggacagaggc ctccttcctc 240

gccagccgcc cgccgcgcct ttcccagctc aggccggcgg cccgcggcgc ggagggagcg 300

aaagagtcgg ggcctgcccc ctccaccgcc cgcatctcgg ccgccgcacc cgggtccgcc 360

ccgggaggcc ccgcgggagg gaacccccgg cccgctgggc gcttccgcac tgacgccttg 420

gggccgcgcg cccccgcccc ttactaccgc tacacccgct gggcccccga ccccgctccc 480

gggctgctgc cagcgccgtc ttcccccgta gaaacttcgg agacacccgg gaagctgctc 540

tttggagttg gggaaactta ggaagaatgg gaaaagccga ggaagtcggg gaggaccccg 600

cagttgcctt gccctcggcc gaaattcctg tgcaattgga cgggaagcct gccacgccca 660

gagagccacc cggtggcacc ccgttgggga cctgcggctg ccctaggctt gagctggcga 720

ccaacggcgc atacccgggg caccctagg ggaccgtgcc cggcccggct tgggggctcc 780

taacgccagg cttgtgagct atagggtgga gagtgggccg gctcttaagg ggaaaaattt 840

gcggcctttt accaggcaca gccag 865

<210> 79
<211> 983
<212> DNA
<213> Homo sapiens 5.D.9

<400> 79
gcggccgcag ccagcgccgc ccctcccggc cgggcgggcc ccaaaagccc tttctgtcac 60

cgcaccaggg cgcgaccggg tgatgcattt ccacaccagc ccgcccaaac ctccatggtt 120

ttggagctcc cgggcaggcg gtggaaactt ggcgcaccgt gcccactctc cggcgccgct 180

ccgacagccc gacgggtccc gcggccagga agccactcgg cgcccctcgc cgtcactcga 240

cccccggccc ctttcggact ccgatcctcc cgtccccagg ccacacggcg cggaaagggg 300

atgccgagcg ggacgcgcac gaccagggcg cccaggacga gggcgctgga ggagactccg 360

ggcagggacc ggggtcccag gggcccgggc cggggctcaa cacccacccg atggggtgcg 420

ggcccgacgg ggcccggggg tgggagtagg ggcggcgggg gcccgcggag gaggagtggg 480

gataggccgc gcaggggggtg cccgggaccc cgggcgcaag ctgggaaaga ggcacgcggg 540

ggcggcgcgc cggggccggg acaggcgccc gtcctcacct gccgggcagg tgtcccgccg 600

gcgagtcgcg cgcgttgctt tccgaggtgg aactgtcgtg gtccacggcg catggcgcgc 660

tgaaggcagc ggccagcagc ttcataaggt cggcggcggg gcaggtgccg gggccgggtc 720

ggaggccacg ccggggccct gggctggggt cggggcgact agcgggctgc gagcgggttc 780

cacgcgcgcg gttcaacggg ctgcacccgc gccgcaccgt gccaacactt cgggcgggcc 840

ccgctgaggc tccggttgcc cgcactagga ggcgagggcc cccgcgtgca agccgccggc 900

ggcgggcccc ggttgccacc ggccccagcc atgggtgggc tccgggttgc tttccccccc 960

tgccccctag ggaattgagc cga 983

<210> 80
<211> 432
<212> DNA
<213> Homo sapiens 5.E.2

<400> 80
gcggccgctg gtgacctccg cccgcggtca ctcgacgccc agccttggcg cgtttgcgca 60

actgcttttg tcccgagcct tcattctggg cgcagtcccc tctcccagtc cccctgccgc 120

ggcgcctgga actctcctgg tggctgtaag attttcctac cgttaggtcg tctgtggcga 180

ccgccaggcc tgccccacat cgctagccgc cctgtctacc cctcagcctc ccagccacta 240

aactcgctgg acaaccttac gctagtaaca gtttttgagt ctcagactca tctgtgaaag 300

ggcagtcata tttgaggact ccaaatgggc tgcagtgcgt aaaccaccat gcgatatttg 360

gttgctattg cccacctcag cctgtggcca atgtgtctct gtaggaacag cactagattc 420

tttggggttt tt 432

<210> 81
<211> 746
<212> DNA
<213> Homo sapiens 5.E.25

<220>
<221> n
<222> (1)..(746)
<223> a or g or c or t

<400> 81
gcggccgcgg gggcgtcagg tccttgcgcc tcctcctccg gctcttcccc cagcctctgc 60

ggggcgtcct ctcccacctc cggggcccac tcctcccccg gagagccccg gggcgcatcc 120

tcaaaagcat cctcctcacc ctcctcatcc gtgtccccag cccctcgcac gggggctccg 180

gccgcttcct cccccggccc ggcctcggga aatgggaaag ccgtggagga gggcgagtct 240

ttggccgcgg gttgcgctgc cgggagactg ggcgcctcgg agaccgggag gccgccgggg 300

gacggcggtt gctggggctc ccggggctcg gcggccaggc tctcgggcag gtcggagagc 360

gcggacagcg cctgctcggt gtccggactg cccggggcct ccccagcccc gccgctcggc 420

cccagcagga accggtccag gcccaggaag gccccgggct gaggggagac ggcagtgggg 480

ggcgctgcag gctcctcggc gccctggagc tgctgctgct gctgctgttg ctggagctgg 540

agctggagct gctgctgctg ctgctgctgc aggcggatcg cctgctggat gtctgaaagc 600

aaatcctctt gctccgtagc cgaatggaag ctatagatgt ccgtgtccga gcccgagctg 660

gtcctttgtc catcctgcgc ccctgctgca gtttncacat cctcggcgat cggccggccc 720

ccgaccctag cctcggcagg cccagg 746

<210> 82
<211> 617
<212> DNA
<213> Homo sapiens 5.E.4

<400> 82
gcggccgcgg gccggtgttt caggcagctc ttgggcgccg gcgggctcgg ggcgggcgcc 60

gtggagggct cggtcccaat tctctcgggc tcggtccccg ctcctctctc gggctccgtc 120

tccgcttctc tctcgggctc aggcgccggc cctgggggcc ccttctcctc atccgggagc 180

acgggcggcg tcggctccgc ttccttcggg acactgcgtt ctggcccgtc gcgagcagag 240

ggcgcctctg aggtggcggc ggggtcagtc tcgggggggag tcgtgtcccc ctcagggatg 300

gcggtgggaa acgggctcgc gacgtcttcg ggagcacaga ccacctcctc cgccttgtcc 360

gtggccgggg cacacgggcc tgcgggggggc gcctccccat cctgctttcc gccgtcggga 420

ccgggattcg gggggccctc cggcggggac gggggctcca cgcggagagt gggggccgac 480

tcgggctcgg cgagctccgg ggtggccggg cggcttgagg ggtcctcccc ggggacgccc 540

ccctcctcca cgctggccgt gagcgcggag gagtgctgca ggcgggcgcg tctggcacgg 600

gcccctccgg gtggcgg 617

<210> 83
<211> 1840
<212> DNA
<213> Homo sapiens A.2.F.45

<400> 83
ggcgcgccga ggcgcaggcg cggagaggcg cggcgctctt ggggagacgc ggcgcagggc 60

atagacgtac gccggcgcct ccccggaggg gaggggtcgc tgggcgggcg ggagtgaggc 120

gcggcgccgg cgcagagacg cacgtcgctg ggctgagggt ggcggggagt gttgcagtcg 180

tacattcgcg cgccgccggg cggggagcgc gggggtggcg cggtgcaggc gcagagacac 240

acgtacccgg cggcgcagag acgagtggaa cctgagtaat ctgaaaagcc cgtttcgggc 300

gcccgctgct tgcagccggg cactacagga ccagcttgcc cacggtgctc tgccattgcg 360

ccccctactg gcgactagga caactacagg gccctcttgc ttacagtgct gtccagcgcc 420

ccctgctggc gccggggcac ggcagggctc tcttgctcgc agtatagtgg tggcatgccg 480

cctgctggca gctaggaaca ttgcagggcc ctcttcctca cattgtagtg gcagcacacc 540

cgcctgctgg cagctgggca cactgccggg ccctcttgct cgcattgtcg tggctgcacg 600

ccacatgcag gcacatgggg actacgcagg gccctcttgc tcccggtgtg acggctggcg 660

tcccatattg gccacctcct gcaccactta aagtcagagc gccagttatt aatccccatc 720

agttctgtaa attaaaactg aaaaggagct attactgcgg agagctgatg tcccagttat 780

taacttggaa gacagctttt caccaagagg cagtacaaag atggaagata acttcattga 840

aaagaaatac agtgtaaaga gcttattgta caaaaatagg gaggagtagg ctgatactgc 900

atgaaaacag cctaagagtc ctgtgcaggg atttttattt tggacttctt cacattccta 960

cctctgtctc aagtctccgc ctgttttctt tggttttcct gctactgcct taggtccccg 1020

acttgcccca cttagccttg tgggacctcc tcacttgatt gaggtacatg tgtggtgatc 1080

aatccgaatc cactctggca ccagcctcct tcccaccata ccaggcaggc tgacagcggt 1140

cacgtttgta tctactgcag ctgcctcttt tgaatgtctt tctctgcctt aatctgtact 1200

tatggtgcca ggtttctctt aagaatgtcc cctttgtcct tcttatcagc atgtagctag 1260

caatattctg acatttttat tgcagaatga atgatgattg gggcttcttt ttttttttt 1320

tttttgagac ggagtctcac tctgtcaccc aggccagact gcggactgca gtggcgcaat 1380

ctcggctcac tgcaagctcc gcttcccggg ttcacgccat tctcctgcct cagcctcccg 1440

agtagctggg actacaggcg cccgccaccg cgccagctaa ttttttgtat ttttagtaga 1500

gacggggttt caccttgtta gccaggatgg tctcgatctc ctgacctcat gatccacccg 1560

cctcggcctc ccacagtgct gggattacag gcgtgagcca ccgcgcccat ccgattgggg 1620

catcttaaga gaagttctag ggtgtttctg cgtaggtacc tcttctccct cctaaccaca 1680

attgacaagt gcccatccac tccagcacta gagatgctac taatatgtgc atttttggtg 1740

gtccctccag gtgagccttc acagactttc ccttttccag gagctccccc tcctgttcat 1800

gtctagctag ctatctactc taacagagcc cactatcctg 1840

<210> 84
<211> 3592
<212> DNA
<213> Homo sapiens A.2.F.50

<400> 84
gccgaggagg cggctccgac ccaggtcgtc gcagcagcac aggaagctgt aacacaggta 60

agtgcaggag agcgagagcg tgaaggcgaa gagcagcctg cgcgccctcc gcggctgagg 120

tggccccgcg cggcccagga ccctataggc catggctcca tgggcccgcg ccgggggtca 180

tggtttccga gggggcaccg gcggctgagc tgctgtggcc ctgcggtcgc ctagagggct 240

cgcgtggcgc tgccacggcc acgcgggtcg ggcgttgggg gcgccgtctt ctccgggggc 300

tgctgaccag ggtgcgcaca gtgccagggg gtcccggggg cagcggctcc tcggggaaca 360

ggcggttgca tttccagcat ctcccggtcc taggcgatgg ggctccgggc agccgggcgg 420

ctcgggcgct cccaggctct tacgtgcgcc gggttcggag cgcgcccagc gcccgaagcc 480

ccattcctga tcctcggagc gccgctcacg aaacgctcgg cggcggcgcg gctgtgcggg 540

ctggcgggtg gaccggacgg tggcgctggc gccggccgcg atctggctct tcgggaaatg 600

ccgagcggag cgcgctgccg gctctattta aggagtggcc tgacgtcagc cgcgcgggtc 660

ccccgagccc gcgccgcgcc cagggacctg gcccgccccc tgcgccccca ctctcttacc 720

cctcccagaa acacagcacg cgggccctcc ccatgcaggc cactccctac ggagccccag 780

gccagctttg gggcggtgaa acgaaggtgt caaggcatag tactcctccg ggaggctgga 840

caccccccacc acgctggcct ctcgacatcc agggacacga atccaggtcg agatcgcgcc 900

gacatgcaga ccagacagac ccagacgcag acgcaggcac cctgccctga tgcgcggtcc 960

caccaccctg acccgcacac gcacgcacag gcacagaagc acacgcgccc tagcccggac 1020

acacccccac acccacgcgg gggtggggag gagaagtccc ctaacctggg cccagataca 1080

ccgacaagga cactcccccc gctctcgaca tctcgccaaa tggacacaca cagcccggaa 1140

tcggacaccg agcgcacgca cgccctggac tgggacacgc gctgtagacg ggatgggtgg 1200

aggagccgag cgtgagtgag attccgtgac tattcaccca gcttcttagc ccccagcgcg 1260

ctgactcaca ccccggcggc tcgctctgtc tcgcacctat gaggcacgcg cgcaccccaa 1320

cccattgtca ccccacctct ccccgggcct gccggagagc gagccccgga gcggcagact 1380

ccgcgtcagg agggttcctc tcttagcagc cgccgcctag cggtagactg ctccccgggg 1440

agctgtccag ggtaccagag ggtcgccgag ggctgagtga ggagggcttc ttcacacaga 1500

gacactagga ggaggaaaca gagtacaagg agaacgtatc caggagcaat tccacttcga 1560

atgattccta agtgaatgcc tacaggacag ttctcggtga ccatgtccag aacaggcata 1620

agtgacgatc cccagtactt ccctgaggga ccacactggt accttggatc agaaccctgc 1680

atcagaacag gcctaaatgg ccatggctaa gaacacggct gagttgtcct tcaacagcaa 1740

tgccaatgcc aattcaccat gtccgagtgt tcacaaggtg agtgccctcc accaccaccc 1800

agccatagaa tgtctagatg accaccatga cccccaccct gatcagggta taactgactt 1860

ccttcctcag gctgtaaact gatcattagg ttctgtggat cttagcccaa accagaaaat 1920

attttgtccc caaactagtc ccatccctag aaaccttaaa ccaattctac ggcagataat 1980

aataatagct gccaactttg tatcaagcac ctggcatggg ttaactgatt aaatattcac 2040

aacctatgaa gttgttacca ttaccctggc atcactttgc tgtcttaatt ctaatagtag 2100

ctagcattta ttgagtgctt gttttatggg agttatgcgc taatcacttg acatgcacta 2160

cctcatttat ctttggagat aggtattatt gtaatttcta atctacaggc agtgataaga 2220

agatttaaca aacatataca cagtaactgg cagagctggg attaaacccg ggcagtcttg 2280

actccaagat tcaagctctt agttacagca ctttgcagct tcctaacttc ctttgaccat 2340

tattcatata attccatcct aggctcctct cctggatgta agctaatttg tctatgtctc 2400

ttctaaaatc tcacacctgg gactgcgcga ggaatttcag atatggattg aaaagttcaa 2460

caggactctc acctctcttt tgtaagttct atttctagta atgccaccta agactccatt 2520

atctttttct tgtggctata tcacactgct gacatctcaa acttgcagcc aagtaacatc 2580

tctaaatgtt tcttacaagt gctgctgatt aaggcacagc taccccatac tgtgcttgta 2640

cagtgggcct ttttggaccc aatgtgtagg tccttataga tttgacttga ttgcatttca 2700

tcttgtctca tcagttcgct gccctagttt tttttaaatg tctatttgaa gtcaaaccac 2760

gaggtagctt tcatttattc aaaaagaaaa agtagaaaga ttgtatccca gctttaccct 2820

ttattccagg tgtactttgg gcaagtggac ccccttaag cctcaggttc ctcagctgta 2880

aaatgggacg ctatgattca ccttaaaagt ctctcaaagt ttagatgttg catgattcta 2940

tgattccatt acccaaagca tgaaccactc acttggcatc atgtaatttc cacagttgat 3000

cacaatttaa ttaattcctc attctaattg ttaataaaaa tgtcaaaaca aatatactta 3060

aaggagttct tcttcttctt ttgggtgagg ggaagtgtct cactctgttg accatgctgg 3120

catgcagtag tgcaatcata gctcatgctg cagcctccac ttcctgggct caagggatcc 3180

tcctgcctca gcctcctgag tagctaggac tacaggcatg tgccaccaca cctagctagt 3240

tttttaattt tttgtagaga tgaagtctta ctgtgttgcc caagctggtc ttgaactcct 3300

gagctcaagt gatcctcctg cctcagcttc ccaaagtgct agaattacag acatgagcca 3360

caatgcctgg cctggaagga gctcttatat atactttgaa caattattca catcatgaac 3420

ctgctatttt tgtattccat tgttaaaatt acaaggttaa atgtggagtc atctgctgtg 3480

atcagtacta tttcccttag aaaataaaac atgaatataa tgatttctca taattctgtg 3540

cttggcttaa tttttaaata atttttaacc tttgaattca taaactgtga ta 3592

<210> 85
<211> 2722
<212> DNA
<213> Homo sapiens A.2.F.67

<400> 85
cgccgccgag gacactcggg cgcacacccg ccgcgctggc gtcccccacc cccagcccaa 60

acaaaagaca agccttgggg tcgtggcctc gctgggccgg ggcgccccga gccggccagg 120

gcgccctctg gggccagagc tccatggttt gcctaaggca tagcttcttg gcggtaggcc 180

gcaagcggcg gggagacgcc aggcagggct gggccgccca gaggtccgaa gatgcctcca 240

gtcgccgccc cggggaaggc gcgggcgacc tctgagtgtc ccggtaacgt gtgcctttgt 300

tccccaactc aggtgaaaat ctggtttcag aacaaaagat ccaagatcaa gaagatcatg 360

aaaaacgggg agatgccccc ggagcacagt cccagctcca gcgacccaat ggcgtgtaac 420

tcgccgcagt ctccagcggt gtgggagccc cagggctcgt cccgctcgct cagccaccac 480

cctcatgccc accctccgac ctccaaccag tccccagcgt ccagctacct ggagaactct 540

gcatcctggt acacaagtgc agccagctca atcaattccc acctgccgcc gccgggctcc 600

ttacagcacc cgctggcgct ggcctccggg acactctatt agatgggctg ctctctctta 660

ctctcttttt tgggactact gtgttttgct gttctagaaa atcataaaga aaggaattca 720

tatggggaag ttcggaaaac tgaaaaagat tcatgtgtaa agcttttttt tgcatgtaag 780

ttattgcatt tcaaaagacc ccccctttttt ttacagagga cttttttgc gcaactgtgg 840

acactttcaa tggtgccttg aaatctatga cctcaacttt tcaaaagact tttttcaatg 900

ttattttagc catgtaaata agtgtagata gaggaattaa actgtatatt ctggataaat 960

aaaattattt cgaccatgaa aagcggaatg tttctgaaaa atacttcatt ctgcccctct 1020

gataactggc tagtgaagtt ttattgaagg caactaaaga aggacaagct ctgcagagat 1080

ccaacaaggc aaaaaagaaa acagaagtcg gggctctatg catgcagact gtatatgtat 1140

atatgttcaa tgctatactt tgtgtgtgtg tgtgcatata tatatataat atatatggca 1200

tgtttatagt actgccatat ctcataattg tttcaggtag aaagtaatgc tgaaataaaa 1260

atacatccct ctcaccctgt atgtgagtta gaaggcaaca gaaatccctc aataacccct 1320

ctgaattcta agctcaaagc aattatcttg gagaagcgcc cccacccatc agcctctgtg 1380

tagtgccaga gcaattagac aaattaccct tcaaagggag tttccagaga tgagaaaatg 1440

aaaaagaaat ctagcctcac acctattaca ttttttaaaa atctaaaatg tttggagcat 1500

ggcaaatgat agaaccttgg actctttgga gtatgattat aaatgtatcg gctcttttcg 1560

agagatgaaa acattgcaga tattgtgaag agggaacttc agggttgggg aaaggaagga 1620

atgaaagcat tgtggcgccg tgttgatttc attttgtgtg agataatact cttaatattt 1680

cccttcccgc cttccttttt tcaggaagga gcttcctctg ttttgctttt acataaaaca 1740

gtggcaaaca ggttctaaat gatgcaaaat agaatctgtt tactaggatt tctcctttgg 1800

gaagccttct ttgggacaga gaggaaggac ttgctgcagc tgtgccctgt gtcccttcct 1860

tcttcttgca ctcctgcatg tagataccaa cagcatgacc agagctatgc actgcaccta 1920

aagacccagg cctgaattgt aggtgtcttt ctgtctggcc gtccttcagt gggccagact 1980

ctctttcctt aggatacgaa ggaaaatgtt gggttggaaa ttacaagatg catgtgaaat 2040

attttacagc taggaagtca gcagcaataa atgtgacaaa agagccttct taaagtgggg 2100

gtagattaga gcataaaaaa ttatatcctg tcactgagga tttctcagaa ggctcttcca 2160

gggttgggag actagacctg aaaaggcacg ctatgtgcct tgaggggaat ttaccttacc 2220

tacatgtttc tctctctgtc tcgtctctct ctcctctctc tctctctttc tctctcattt 2280

tctctgtctc tctgcctgcc tcctcctcct cttctctccc tacctccctt ccacctcctt 2340

tatttttttc gttctcttct cctttacttt ttttctagaa gagttaccag gcccgccagt 2400

gtggaacagc ttgcttcttg gaggaatcag tattttgacc gctctttaga catatcccgc 2460

agcctggctc cgaggcagaa ctacgcccgg cagcctggcc tgtgcacccc tcctccggca 2520

cccccagcgg ccgcgactca atatttccgt ctccccagtc cgctccagcc gtactttctc 2580

ggaaggagca ctgggtgcgg ggaagagggg gcaataggaa ggtttgcggg gggcgggggg 2640

gggggcggga agccaaaggg tgccccattt tgttttctgc gctcacagag aatagggggа 2700

ttggggaaga gatgaagata tc 2722

<210> 86
<211> 3366
<212> DNA
<213> Homo sapiens A.3.F.38

<400> 86
ggcgcgcctc cagttccaag gccgagctca ctttcaacag ctctggaaat atgaatgtat 60

ttttcccccc tttagaagaa gctatacgag gaacaacttt ttgaaatcgg gagtgtgttt 120

gtagagaagg agataaggat tgcatttcgc ttatttttct acaggtgata gaagtgtttt 180

gggggtcaga gtatcctctc aaggaaaatg taaaacgtgg gggctcgcat tctctatcta 240

agcctttgta agtttaatta acaggaccct taaagtattc cttatagcta cagataaaaa 300

attacaggca atgtttggat aaggggccaa ctctccgtgt ccaaacattt agagaactgc 360

ctgtgagtgt acaccgttgt aatcttattg ggagcccttt gtcgaattct gtattttact 420

ttgatgcttt ttgagtacca ttcccattgt ttgggtgtcc tttaactccg tttacagcaa 480

tatattaata aagaggatgc atatgtcagc gttatgtatc cacaagaatt tggattcctt 540

taaaatcaaa cggcttggtg agcaggcaag cactcaaaac ccaacagtct caaacagcaa 600

taataatgtc agcaaacggc tgccatgcct ccttttctcc aaatgctgtt tattctaaaa 660

tcaataagtt aggagataca ttgcagagaa acagtcatta gtggttcagg gttggcaggt 720

ttgtttttca ggtgtagatg ttcttgagta atacctctcc actgtggact aaatattagt 780

agattgtcgt tgtcattttt ctaatttaat gcggcagcct cagggaagta ctcatccaga 840

caattatggg gtatcgattt ttaactttaa gattaaaaaa ataccatatt tcacttgcct 900

tgggactact tttcttgata aaaatatatc tgggaagatg attttagggc catgttagcg 960

taggggaggg gaattaaggc acaaatggtg gttggttaag gaaatttttat gaaagaaaat 1020

aaagaaaaca tgtcagaata aatcaatcag aggcacaagt gagttagagg aatctgagga 1080

caaccagcat cttggggatt cttctgttcc cgcggttctc agatatagga ataagggtct 1140

gagttatgcc cagaatacat tcgtctggta ctggatgtcc cagtccctta gctgttccac 1200

gtaatgaaga agctctaatt cccgagaact ttggggctta tttttaccat cattgagtct 1260

gcccaggctc agctctctta caaaggtata aatctgaaat tcatgtatta atttgaatcc 1320

ccaagatccg agttatgaga aagggcaagg gcaggctcta ctcctatttt gtttactttc 1380

accgagttac tgtgaagtga ttggaaactt tcttaacggg cagagagaga atacacggaa 1440

actcggatgc agtaataaag ttgacatagg agtcggaaca gggggctctt tttggatctc 1500

acctttactg gggcttgagg ttgtggaatg ggtggaagag taattaactg aatgaagaat 1560

tttaacgttg aaaacagagc ccacagtatt tttggttata gtggtgtggt ctctgcctcg 1620

gcaaagaaac aaacaccccc accccatctt cgcagttctc ctctctgctg tagcgacgcc 1680

aggcgctgct ttccgccggg taaattagcg gcgagcctcg ccagacgctt tcctccttgc 1740

cttctttcgc cgaaaggggg cgcgctcctc ccaggctgcg ctggtaccta tcctgccttc 1800

aaaaatttct gggttcctgc aggacagaca gtaacaaaac gtgggaaata atagtttgat 1860

gacacttcag ggactatagg aatataaggt gcacacacat gcatcttaat ggaaacatgt 1920

agacacctgg caggagcatt ggctgcctgc ctctcctcct ttcaaatgag ggtggtcggg 1980

gttccagggt ggcaggaggg gagtggggcc agatgaccgt ggatggaatt ggtgggtgct 2040

aggactgacg cctgggttcc atggcggagg agagggtttg tccccatgga gctgtgtgga 2100

cttttctgca tatgtacttg aggtcttcaa agaaagaagg gcagatctga gaaatggaga 2160

agtggctggt attagtgaga tgttgaaaaa ctgccacaga agccctcaca gtgcctggag 2220

tgttaagaca gaagagaaaa cctggcacca tagagtttta ggccctggga tcagggtaac 2280

ctttcctcct cacgaaagaa caataactgc cccaaatctt gtgtgagcct gcaacttggg 2340

tacctaaagc catttccaat ctgcaaatct gactcctggc ctccactgat cctccatttt 2400

tgggcaagag tttcaagaga ctcacaggac agatgaggat aaatttttaa ccccttctgt 2460

aaatttaggg attttcgact tcttaccact ccctgacaat gggggtcaac aaatcaaggc 2520

acggtgagag taacaaactg gaataatata tattttgtct tcatagcata gatgatggtt 2580

aatacatact ttccaagata atctgagctg gagtgttcac tagaaacagg agcacaaggc 2640

cagaactgta aggcaaattg ctttcccaca aacgtttgtc tgagaataag aacattcacc 2700

ccattcactt aatttctcat catcagtcat gtcattatat tttcaaggac ctcacagtgc 2760

tggaaagtgg tgtagttata aataagcata aaaacagatg ggtgatccca gtcctctaaa 2820

tataatcggg gatgccaaat cttttcaaag agaattcata tatacaactt aaaggccaag 2880

gagcccaatt caatcaaaat ttgagccagg atatgctaag ttcaatcagc ttgaatatgg 2940

gcaaagtgta agacctagcc agcacttcag atatatacag agaaccacat tttctcaagt 3000

ttccattgtt attttccaca caaatttagt gttagtcttc aaagggattg ttagatttgg 3060

tttgggccgg gagggtggtg agagtcagtg ccccaggctc ctgtccttgt ctactcccct 3120

ttctttggta ctctctctgc ttcagcagtt tgccgaaaat ctgtgttgca gagaaaattg 3180

acacctagag gccacagagg tctcctaaat gctgttttct aggatcctca gaaaacaaga 3240

ggaccgctga gctcaattat atgtaatata cctggtatct ttatgtattt ttcttttctg 3300

ctaattcatt ttataatagc taagttagag acttcttgga gatttaggtt ttggggactg 3360

gatatc 3366

<210> 87
<211> 638
<212> DNA
<213> Homo sapiens A.4.D.30

<400> 87
ggcgcgcctc gcccgagatg cccctgcgtc cgcctggcca ggcctggggg ttacccgacc 60

cgggttctcc cttcgctggc tttgcgcccc ttcacacctc tgcggtgggg acggagctgc 120

cgagacaagc agagtgcgaa ctggagaaag cccagagctc agagctccca ggagcccacc 180

gtgccccacg gctaggcggt ctcctggtgt ggacggctag cggtgtcatt acttcttaca 240

aaagtttatt tttgaaagct tctcccttcc ttccttcttc ccttcctttc ttttcttcct 300

tttttctttg ttttgagtca ggttctcact ctgtcgccca ggcaggagcg cagtggcgct 360

atctcagctc acggagcctc cacctattgg gctcaagcga tcctcccacc tcagcctccc 420

gagtagctgg gaccacagtc gcacgccacc acgtccggct aattattttt tttcgttttt 480

cgtagagagg gagtgtcgtt atgctgccca ggctggtttc aaactcctgg cctcaagcga 540

tcctcccacc tccggcttcc caaagtgctg ggattcgggg tgttagccac tgtcccggac 600

tacttctttt ttatcctgtc agaaaaacta tccatgtt 638

<210> 88
<211> 1860
<212> DNA
<213> Homo sapiens A.4.D.36

<220>
<221> n
<222> (1)..(1860)
<223> a or g or c or t

<400> 88
ggcgcgcctg tccccaccta atgccacgat ccnccccctcc cccaccctnc cgcactgcct 60

cccttgcgcg tgtaggggag atccctgacc ttgtctgccc agctgcaggc cacttgccca 120

ggcggccccct cccttgttgc cacctcccgc ccagctcacc aggagcgtgt gccctgttgc 180

tactggcaac tgcctgtgcc taaagctcag cccccaaact ggcttaatgc tgattgatgg 240

tcagaaatag gatattttct ggaacagagc ggagcgctgg tgcaaggccc tctctgctgc 300

tgagtcctag ggacctcccg ggtggcaggc cttcctcctc ctctcctttt ggccccaccc 360

accctacact acccctcaga gaccaacggg ctcttcggac atcctcatct caggttaagt 420

gctgagccag caagccagtg ttcgctttct tgctgagtaa caggcagcca ccccggaatt 480

tctcttctta tccttgaggc ttctgagttt tatgaatgag gcccgtgttg ctggacgcta 540

ccacttccct ttttattttc atccccacta acttgttcac tcgttcactc ctccttatac 600

ataggtacct aaaatagact acccctctag taaccagaac tattcctgca aacgcttaca 660

agagcatttt ccagaaataa atcatttcat atcagtatcc cttcctcagt catttcccgg 720

cttcatgcca cctccctcct aagacacaga attggtcatt tccaccactt taaagacaca 780

gtctagataa aaagcctgca tttataatgt tctttgcagg agtagctttt gcctattttg 840

tgggggtttt gtttgttttt tgttttctgt ttgatactcc ctctcaaact gcagcctccc 900

ttccctttc tgggatggca gcctccttct ctgagccatc ctggactaac attttctgga 960

ctaataaatt tctgcacctg tctctactcc ttctccttcc cagtctgact gtaaaggacc 1020

agatttcatt atcaaatcaa ttctctttag aagaactttg ttctgtagca tttctttcca 1080

ggaccccaat atttttggca gagtattttc attatttaaa ttgtcgtact tagcttcttt 1140

ttgcctatgg acattacttt ggaaaaccat gtgatgtttc tgagtcactg atttgttcct 1200

ccaaacaaaa cttccttcag aggctcccat atgttgggca ccattgtagg cccccggggg 1260

tgggaatgga gcaaagacaa gacccaaatg ggtttcagca ttttaaagcc cccattacag 1320

ctggtttatg gttattgcta tgatggttaa tgtgataaca gcacactaca tttgactagg 1380

actttacagt ttacaaaagg ctttcaaaga cattatctcc attaatccca gcagcaggaa 1440

ttttaaatag caaggattcc accaaaaggc ccagtaatgc tcaccaatcc tgcttaacca 1500

aaaagaaaaa tattgcaaat catcctaaca gctgatggag ctttaaaaca cagaataaac 1560

aattcataag aagcttctga agcttagtta ctggaatgta acttggagaa gataagtgaa 1620

atgcacgtaa catgtatatt accagaaggg tgtcttggag agaaactcca tcctggggct 1680

tcagtggcct ggtgaactgc tggaggtgga ggctttccag ggctctggac tattgcctta 1740

tcctaggatc taaaatggga tgaaagtgtt agcacaaagt tgctgggaga ctagcaaatt 1800

aagcaaaatg agtaggcaat gatgttactt tctttagcta caaagcattc ttgagatatc 1860

<210> 89
<211> 2107
<212> DNA
<213> Homo sapiens A.4.E.32

<400> 89
ggcgcgccac aaggccgtgg tgctgcgctg ccacgctgtg ctgctggcgc gggcgcacaa 60

ggcgcgcgcc ctggcccgcc tgctccgcca gaccgcgctg gcggccttca gcgacttcaa 120

gcgcctgcag cgccagagcg acgcgcgcca cgtgcgccag cagcatctcc gcgctggggg 180

cgccgccgcc tcggtgcccc gcgccccact gcgccgcctg ctcaatgcca agtgcgccta 240

ccggccgccg ccgagcgagc gcagccgcgg ggcgccgcgc ctcagcagca tccatgagga 300

ggacgaggag gaggaggagg acgacgcgga ggagcaagag ggaggagtcc cccagcgcga 360

gcggccggag gtgctcagcc tggcccggga gctgaggacg tgcagcctgc ggggcgcccc 420

ggcgcccccg ccgcccgcgc agccccgccg ctggaaggcc ggccccaggg agcgggcggg 480

ccaggcgcgc tgagagccga aggacaggac tcgcagcccc aggcccgacc cgccagactc 540

acagcctcca accccggccc tgcccgcttc ggctgccccg gcccccggcc cgtgtctccc 600

ccgtggtctc cgtgttgtcc gccccgccgc ctcattttgg ctcaaggtga tgcctgatac 660

gcccttggtt attgggggt gttcctctct ccccacaccc ggagtttccc gggcctgcca 720

ttgtggaccc gccccctatg ctttacacct agtctctttg cccacagacc tcctcattcc 780

ctcccaaaac atcctctcaa gagaagggag gagaagtttc aagaaatcag gaggggtggg 840

tttggaccct gggcagggtg gaggcagtga ccttgccctt ggtccctcta gccttcttcc 900

ctgtgcaaaa aaaaatgacc ctggagaggc attcttgtag gagaagaatc tagcggccgg 960

ggagaattgg ggccgggccg gcggtgggca gagtccgctg ctatacacac agggaggaat 1020

tctcacgccc aagccccgcc tctctacgcc ttggaggact cctgtgactt cactgctctg 1080

cctctggaga acactgggag agtcctaccg acgttcaaac aacaggttag gccaggtaac 1140

agccctgcac caggccgctg cccacgcctc tgccctggca cccccagggg attccttgcc 1200

catcccatct ctctgcagac ggatgtgtgt ggcccccctcc taggtgcccc acaaccagga 1260

ccaagatggg gctcccaaag gaggtaagga gaacctttgg caggtgctta ggacactgac 1320

tacctagaaa gtagacgcag cagagttgct cccaagtcga ggctcctcag agcaggtggg 1380

tcctgacagc agtggattct cccagcagga tgaggaagga gggtgtgtta accaaccaag 1440

ggagtgggcc ccccacccag gtgtctccgc aagaccacaa aaagcccaaa gatctatgtg 1500

tcactgatca ttgtaaataa agtggacctg cttttacagc cctgtcacta ctcctgtgtt 1560

gtgtttaatg ccaggcctgc tgggggtgaa aaaatggatt gaagatcaga taagccacag 1620

gtgagcctgt atagctcccc ctggttacca tcagaaacct gaaagtagtt cttttgagca 1680

gccagagcca accccaggat taggacggga tctggggact gctgccagga agctgttcct 1740

taatgtcaga gaaggaggca gtaacttatg ccttgtctga aaatcacatg tgccaggctc 1800

cctggaggga cgtcggctgt ctgtctcagc ctcccaggat gtctgtacgc ctgggcactc 1860

agatgcaggt gtctgggaca tttggcaggg agggagcact gggctggggg cttctcataa 1920

gcatgtattc atatctctga gaaggttcat gtgtatttca gagcatatgg tatagactgt 1980

gtgtgtgctc tcagggatga gtgcgagcag gttgtaagag aatgtggtga gcagcccagt 2040

tttctttcag aggctctgga aaaacctgtc cagaccctgt ggcagtgtga gtcttcagct 2100

ggatatc 2107

<210> 90
<211> 498
<212> DNA
<213> Homo sapiens A.5.E.28

<400> 90
ggcgcgccgg agttcgggct gccggctcct tagccgcggg gcgggggaga cgctcgggga 60

aggggagagg cgcgggcggg tgggaacggg cgggagacga gcggggacgg ggagacgcgc 120

cggaggcccg gagcccgcgc atgctcagtg cgcggccgga ggaggcgagc gctggggacg 180

cagcacctgc cccgcgcggc cgagaggcgg cagccccagg tccccagcgc gcgaaattag 240

taaagggcgc ctggcccgat tctcaggcaa gaggagatta tcagccggat tcccgtgcgg 300

ggacgtaggg gttgcgttgt tcagcggcca gggatgcgcc gaggcgatgt ctcctccctt 360

tacaacccga gtatcggggc acgaggaggc gcgaccttcc tgggtaccca aacctctggc 420

ctccgggaga cgcggaattc gggggatcgt taaggcgccc tggccaggga aacagatgct 480

tctgcgtctg ggctgaaa 498